Archives of Internal Medicine

VOLUME 41 JUNE, 1928 NUMBER 6

ANGINA PECTORIS

A SYNDROME CAUSED BY ANOXEMIA OF THE MYOCARDIUM [1]

CHESTER S. KEEFER, M.D.
CHICAGO
AND
WILLIAM H. RESNIK, M.D.
STAMFORD, CONN.

CONTENTS

Introduction
Definition of Angina Pectoris
Pathogenesis of Angina Pectoris
Pathology of Angina Pectoris
Critical Review of the Prevailing Theories of Pathogenesis of Angina Pectoris
Cause of Pain in Angina Pectoris
Cause of Sudden Death in Angina Pectoris
Angina Pectoris and Coronary Obstruction
Angina Pectoris and other Types of Cardiac Pain
Consideration of Certain Problems Concerned with the Anoxemia Theory of Angina Pectoris
Summary and Conclusions

In spite of the fact that angina pectoris has been known for over a century and a half, there is still a lack of unanimity regarding its cause. In this paper we will present a theory which, we believe, offers a logical answer to the problem. It is not our purpose to make any pretense at a comprehensive review of the extensive literature dealing with this question. We shall limit ourselves more or less closely to a consideration of those facts and views concerned with the problem that conform to the present ideas of anatomy and physiology.

DEFINITION OF ANGINA PECTORIS

In a discussion of angina pectoris, it is absolutely essential that there be a clear understanding of what is meant by the term. No doubt much of the confusion concerning the nature of the condition has been due to the absence of a well recognized and uniform pathologic basis for the condition. This state of affairs has permitted a certain degree of looseness in the clinical conception of the condition, since no absolute criterion was at hand even at autopsy to prove whether angina pectoris

1. Read at the New York Academy of Medicine, Section of Medicine, April 17, 1928.

had or had not been present during life. The result has been the inclusion under the term angina pectoris of cases which differ considerably among themselves, and which often have as their only common feature the occurrence of pain or discomfort in the region of the heart. Expressions like "pseudo-angina," "reflex angina," "vasomotor angina" and "secondary angina" have been coined to cover the various types of cardiac pain which bear more or less resemblance to the "true" angina. To some, angina pectoris is practically synonomous with "heart pain," merely a symptom complex elicited by a wide variety of conditions. To them angina pectoris does not stand for a clear and well defined clinical picture; at times it may have the terrible significance that is commonly attached to the term; at other times it does not have any other significance than the expression in pain of an entirely benign condition.

We feel that such a conception of angina is entirely erroneous. The fact remains that out of the confused mêlée of clinical conditions to which the term "angina pectoris" has been applied, one condition stands forth, clearly marked from the others. It is the one that corresponds to Heberden's original description, and its import is unmistakable: the patient with this condition is doomed.

> But there is a disorder of the breast marked with strong and peculiar symptoms, considerable for the kind of danger belonging to it, and not extremely rare, which deserves to be mentioned more at length. The seat of it, and the sense of strangling, and anxiety with which it is attended, may make it not improperly to be called angina pectoris.
>
> Those who are afflicted with it are seized while they are walking (more especially if it be up hill, and soon after eating), with a painful and most disagreeable sensation in the breast, which seems as if it would extinguish life, if it were to increase or to continue; but the moment they stand still, all this uneasiness vanishes.
>
> In all other respects the patients are at the beginning of this disorder, perfectly well, and in particular have no shortness of breath from which it is totally different. The pain is sometimes situated in the upper part, sometimes in the middle, sometimes at the bottom of the os sterni, and often more inclined to the left than to the right side. It likewise very frequently extends from the breast to the middle of the left arm, as I have had opportunities of observing by feeling the pulse during the paroxysm. Males are most liable to this disease, especially such as have passed their fiftieth year. After it has continued a year or more, it will not cease as instantaneously upon standing still, and it will come on not only when persons are walking, but when they are lying down. . . . Some have been seized while they were standing still or sitting, also upon first waking out of sleep. . . . The termination of the angina pectoris is remarkable. For if no accident intervenes, but the disease go on to its height, the patients all suddenly fall down, and perish almost immediately.[2]

In this masterly description of Heberden's, are found the essential features of angina pectoris. It is the condition depicted therein that we

2. Heberden, William: Commentaries, p. 292.

wish to discuss, and to which the term "angina pectoris" rightfully belongs. It is characterized by (*a*) paroxysmal pain, usually pectoral, provoked by an increase of the demands on the heart and relieved by a diminishing of the work of the heart, and (*b*) the likelihood of termination by sudden death.

The pain is brought on by effort. By effort, we mean anything that demands more work of the heart than is imposed on it at rest. This may be actual muscular exercise, such as walking. Since climbing an incline places a greater burden on the heart than walking on a level, the pain usually shows itself first when the patient mounts a flight of stairs or climbs a hill. The pain is even more easily produced when the muscular exercise is undertaken against a wind, in the cold or after a hearty meal. Emotion alone may precipitate an attack. But whatever may be the stimulus that calls forth a paroxysm of pain, it is always one that increases the work of the heart. The pain is usually substernal, but it may be referred to the precordia or epigastrium; it often radiates to the upper extremities, or jaw, or to more remote areas of the body, and may, indeed, be felt only here. Early in the disease it may be described as a sense of oppression, but when it becomes well marked, it is, characteristically, constrictive. The pain is rapidly relieved by rest, and is often accompanied by a sense of impending dissolution, the "angor animi" on which so much stress was laid by Allbutt and Huchard. The anguish is described (Allbutt [3]) as being "even in slight or incipient cases, an organic dread or sense of ill-omen, as contrasted with rational apprehension," "a strange indescribable fear."

The condition is likely to end in sudden death. Any hypothesis that attempts to explain the nature of angina pectoris must account for this remarkable feature of the disorder. The likelihood of sudden death is the one distinguishing feature that differentiates "true" angina from all forms of "false" angina. The lack of appreciation of this point as a cardinal characteristic of the disease has led to the confusion of Heberden's angina with other types of cardiac pain that should never have been called angina pectoris. The likelihood of sudden death is a feature that is indissolubly linked with the underlying mechanism of the disease. Only by including in angina pectoris such cases as are "likely to end in sudden death" does one isolate those cases that correspond to the original description of the disease, and eliminate the cases that bear only a more or less close resemblance to Heberden's angina. It is, of course, impossible, in a given instance, to predict with absolute certainty the ultimate outcome of the case; but when the diagnosis "angina pectoris" is made, there should automatically be the implication

3. Allbutt, Sir Clifford: Diseases of the Arteries, Including Angina Pectoris, ed. 1, New York, The Macmillan Company, 1915, vols. 1 and 2.

that the patient may, and probably will, die suddenly. We shall later explain in more detail our reason for making the likelihood of sudden death such an integral feature of the definition of the disease.

The foregoing characteristics, then, are those that distinguish angina pectoris from other types of cardiac pain. It must be stated that certain exceptions exist. On occasion, the pain of true angina pectoris may arise spontaneously, as during sleep; that is to say, without provocation of one of the usual stimuli: muscular effort, cold, emotion or a hearty meal. But even these exceptions are probably more apparent than real in many cases. In some instances, the pain may not subside on rest, or the outcome is not sudden death. In fact, actual cure may take place. These exceptional instances will also be discussed later.

All the other manifestations that may occur in angina pectoris are of minor importance: changes in respiration, in blood pressure, in heart rate and rhythm, in the vasomotor system, of posture, etc. They are inconstant and do not belong to the major picture.

THE PATHOGENESIS OF ANGINA PECTORIS

It is our belief that angina pectoris is always due to anoxemia of the myocardium; that is, the attack occurs when the oxygen supply to the heart is inadequate to meet the oxygen demands of the heart. In the usual case of angina, the anoxemia is relative, being sufficient for the needs of the heart at rest and insufficient when the work of the heart is increased. In acute coronary occlusion, however, the anoxemia is absolute, since the oxygen supply is inadequate even when the heart is at rest.

All cases of genuine angina have anoxemia of the myocardium as their basis; nevertheless, anoxemia of the myocardium may exist without causing angina, and it must be confessed at once that all factors determining whether or not angina will develop are not clear. Thus, anoxemia may be present in congenital heart disease or pernicious anemia, for example, and yet angina is extremely rare in these conditions. It would seem that when anoxemia affects all the tissues of the body as well as the heart, or when the heart is uniformly affected, so far as one may judge, angina is usually absent. When the heart is affected in such cases, the symptoms are practically always those of so-called congestive heart failure. On the other hand, angina tends to appear when, in spite of anoxemia being present, the contractile power of the heart remains good, evidenced by more or less complete freedom from dyspnea or other symptoms of a failing myocardium. These conditions occur most commonly when only a restricted part of the heart muscle suffers from lack of oxygen, as in coronary sclerosis; the remainder is relatively uninvolved and hence the contractile power of the heart remains good. There are exceptions to these rules: there

are rare instances of angina pectoris in patients with pernicious anemia; and a patient with coronary sclerosis may suffer only from so-called congestive heart failure, angina never appearing.

The idea of anoxemia as the cause of angina is not new. All coronary theories are based on the contention that ischemia of the heart muscle is the cause of angina. "An author who would wish to appropriate for himself, with respect to the priority of this (coronary) theory, the labor of a whole century, would commit an injustice for his own profit" (Huchard [4]). However, the idea of coronary spasm has been incorporated in practically every recent theory that attributes angina to ischemia, and we shall show that such an idea must be regarded with skepticism. It is possible, however, to demonstrate anoxemia in all genuine cases of angina pectoris, without resorting to a theory of such questionable validity.

THE PATHOLOGY OF ANGINA PECTORIS

The pathologic conditions associated with angina pectoris may be grouped as follows:

1. Coronary disease.
   (*a*) Sclerosis of the coronary arteries, with or without complete obstruction.
   (*b*) Occlusion or encroachment of the mouths of the coronary arteries by either syphilitic aortitis or arteriosclerosis.
2. Aortic insufficiency.
3. Miscellaneous conditions.

Coronary disease and aortic insufficiency make up the vast majority of cases, as will be seen from tables 1 and 2.

Of the cases of angina pectoris that we have personally observed, thirteen have come to necropsy; table 1 summarizes the pathologic observations. All the patients had either coronary disease or aortic insufficiency: five had coronary disease alone, five had aortic insufficiency alone and three had combined coronary disease and aortic insufficiency. Table 2 gives the important pathologic data in other series of cases taken from the literature, and again the preponderant rôle that coronary disease and aortic insufficiency play is well illustrated.

Coronary Disease.—But few words need be devoted to the subject of coronary disease. Aside from the question of involvement of the aorta, there is not any doubt that the commonest lesion by far in cases of angina pectoris is coronary disease. This fact is sufficiently well recognized to render further comment unnecessary. The production of anoxemia of the heart by such a lesion is, of course, clear. We merely wish to call attention to the important work of LeCount [5] who

4. Huchard, H.: Traité clinique des maladies du coeur et des vaisseaux, Paris, 1893, p. 610.

5. LeCount, E. R.: Pathology of Angina Pectoris, J. A. M. A. **70**:974 (April 6) 1918.

reported sixty cases in which death resulted from disturbance of coronary circulation or from lesions generally regarded as caused by such difficulty. Of 175 patients who died from heart disease, only those with coronary disease had had symptoms indicative of angina pectoris.

TABLE 1.—*Authors' Cases of Angina Pectoris; Observations at Necropsies*

Conditions Observed	No. of Cases
Coronary occlusion of one of the main branches	4
Extensive coronary sclerosis without complete occlusion	1
Syphilitic aortitis with aortic insufficiency (occlusion of the left coronary ostia in 2 cases)	5
Rheumatic aortic insufficiency (one case complicated by subacute bacterial endocarditis)	2
Aortic stenosis and insufficiency with narrowing of coronary orifices at their origin in the aorta	1
Total	13

TABLE 2.—*Pathologic Observations in a Series of Cases Taken from the Literature*

Author	Total Cases	Coronary Disease	Aortic Insufficiency	Remarks
Huchard: Traité clinique des maladies du coeur et des vaisseaux, Paris, 1893, p. 610	145	145	Not mentioned	
Osler: Lancet **1**: 697, 839 and 973, 1910	17	14	1	(a) One case. Coronaries were "small" (b) One "negative" case
Thayer: Internat. Clin. **1**: 1, 1923.	24	19	Not mentioned	(a) One case with myocardial scars (b) Four cases with syphilis of aorta the only obvious lesion
Mackenzie: Angina Pectoris, London, Oxford University Press, 1923	22	18	5	(a) Two cases with muscular changes such as one encounters in coronary disease. Exact state of coronaries not given
Braun: Wien. klin. Wchnschr. **39**: 265 and 304, 1926	127	127	—	
Oberndorfer: München. med. Wchnschr. **72**: 1495, 1925	17	17	—	
Gallavardin: Les angines de poitrine, ed. 1, Paris, Masson & Cie, 1925	14	13	0	(a) One case with "azotemic" nephritis
Pauli: Ztschr. f. Kreislaufforsch. **19**: 169, 1927	20	20	2	
Present series	13	8	8	
Total	399	381	19	

Aortic Insufficiency.—Although aortic insufficiency ranks far behind coronary disease in incidence, this lesion is found in the bulk of the cases of angina pectoris not associated with coronary disease. Often the two conditions occur together, particularly when both are caused by syphilitic aortitis. The striking frequency with which aortic insufficiency is accompanied by angina has long been recognized and emphasized by

Nothnagel,[6] Neusser,[7] Fraenkel,[8] Osler,[9] Gallavardin,[10] Longcope,[11] Mackenzie[12] and others. Lord[13] stated that in five of his six cases of angina occurring in syphilitic patients there was aortic insufficiency. Gallavardin found that of his cases of angina with aortic insufficiency, 87 per cent were of syphilitic origin.

Mackenzie observed angina pectoris in ninety patients with aortic insufficiency, 23 per cent of the total number of cases reported. It is not clear how many of his cases were due to syphilitic aortitis. In some, in which postmortem records are available, the coronary arteries were normal; in others, some degree of obstruction of the coronary arteries was present, either by narrowing of the orifices or sclerosis of the vessels. Of our own cases of angina, seven occurred in patients with syphilitic aortic insufficiency. Of these latter patients, five came to necropsy, and in two there was partial occlusion of the coronary arteries. Among other authors who mention the occurrence of angina in cases of syphilitic aortitis and aortic insufficiency may be mentioned Longcope,[11] five cases, and Lamb,[14] ten cases.

Although it is true that when angina pectoris develops in a patient with aortic insufficiency, the valvular lesion is usually of syphilitic origin, angina is also seen in instances of rheumatic aortic insufficiency. We have observed four patients with this type of valvular disease who suffered from seizures of angina; in the one case in which necropsy was performed, the coronary arteries were patent. In a group of thirty-three cases of aortic insufficiency in young persons, in which the history of rheumatic infection was positive in 87 per cent, Clark[15] found that "many of the patients suffered from attacks of angina pectoris." Allbutt referred to similar cases, and other instances were recorded by

---

6. Nothnagel, H.: Schmerzhafte Empfindungen bei Herzerkrankungen, Ztschr. f. klin. Med. **19**:209, 1891.

7. Von Neusser, E.: Angina Pectoris, New York, E. B. Treat & Co., 1909; trans. into English by Andrew MacFarlane.

8. Fraenkel, A.: Angina Pectoris, Kong. f. inn. Med. **10**:228, 1891.

9. Osler, William: Angina Pectoris, Lumelian Lectures, Lancet **1**:697 (March 12) 1910; **1**:839 (March 26) 1910; **1**:973 (April 9) 1910.

10. Gallavardin, L.: Les Angines de Poitrine, ed. 1, Paris, Masson & Cie., 1925.

11. Longcope, W. T.: Syphilitic Aortitis: Its Diagnosis and Treatment, Arch. Int. Med. **11**:15 (Jan.) 1913.

12. Mackenzie, Sir James: Angina Pectoris, London, Oxford University Press, 1923.

13. Lord, F. T.: Discussion, Tr. A. Am. Phys. **42**:53, 1927.

14. Lamb, A. R.: Syphilitic Aortitis and Aneurysm of the Aorta in Nelson's Loose Leaf System of Medicine, New York, Thomas Nelson & Sons, 1924, vol. 4, p. 531.

15. Clark, J. W.: Some Features of Aortic Regurgitation in Young Subjects, Brit. M. J. **1**:1364 (June 10) 1911.

Coombs,[16] Levine,[17] Gallavardin,[10] Cutler and Fine,[18] Wenkebach,[19] White and Mudd [20] and others.

Angina has also appeared in rare cases of rupture of the aortic valve (Hirschfelder [21] and Herrick and Nuzum [22]). In Hirschfelder's case, the coronary arteries were normal.

Various hypotheses have been advanced to explain the occurrence of angina in cases of aortic insufficiency. Since most of the cases were associated with syphilitic aortitis, the latter condition was held responsible by Allbutt for the attacks of angina. Nevertheless, he confessed that he was unable to account for the angina in instances of rheumatic aortic insufficiency in which the aorta was normal. Fraenkel held that changes in the intraventricular pressure probably played a rôle in causing the angina, and Mackenzie attributed the attacks of pain to some peculiar innervation of the heart in aortic regurgitation. None of these explanations are satisfactory or based on fact. We feel that modern experimental evidence has furnished a more logical explanation for the occurrence of angina in cases of aortic insufficiency.

Lewis and Drury [23] first demonstrated that the circulatory changes taking place in arteriovenous fistula were similar to those seen in aortic regurgitation, namely, low diastolic pressure, high pulse pressure, water hammer pulse, collapsing pulse, etc. They presented evidence to show that these signs were dependent on a leak of blood from the arterial stream and suggested that the same was true in cases of aortic reflux. Since the coronary blood supply is dependent for the most part on the height of the diastolic blood pressure, and since in aortic insufficiency the diastolic pressure is characteristically decreased, it was reasonable to suppose that a diminished coronary flow was present in cases of aortic

16. Coombs, C. P.: Rheumatic Heart Disease, ed. 1, New York, William Wood & Co., 1924.

17. Levine, S. A.: Angina Pectoris (Some Clinical Considerations), J. A. M. A. **79**:928 (Sept. 16) 1922.

18. Cutler, E. C., and Fine, Jacob: Sympathectomy in Angina Pectoris, J. A. M. A. **86**:1972 (June 26) 1926.

19. Wenkebach, K. F.: Angina Pectoris and Possibilities of Its Surgical Relief, Brit. M. J. **1**:809 (May 10) 1924.

20. White, P. D., and Mudd, S. G.: Angina Pectoris in Young People, Am. Heart J. **3**:1 (Oct.) 1927.

21. Hirschfelder, H.: Diseases of Heart and Aorta, ed. 3, Philadelphia, J. B. Lippincott Company, 1918, p. 388.

22. Herrick, J. B., and Nuzum, F. R.: Angina Pectoris, J. A. M. A. **70**:67 (Jan. 12) 1918.

23. Lewis, T., and Drury, A. N.: Observations Relating to Arterio-Venous Aneurysms: Circulatory Manifestations on Clinical Cases with Particular Reference to the Arterial Phenomena of Aortic Regurgitation, Heart **10**:301, 1923.

insufficiency. However, it remained for Smith, Miller and Graber [24] to demonstrate that the coronary flow was actually decreased in experimental aortic insufficiency in dogs, and that this decrease was caused by the lowering of the diastolic level. We have, then, definite proof that in aortic insufficiency there is a diminished blood supply to the heart muscle, satisfactory grounds for assuming that anoxemia of the myocardium may ensue.

We shall point out later that the greatest stumbling block in the way of acceptance of the "coronary" (ischemia) theory are the cases in which coronary obstruction—that is to say, ischemia—cannot be demonstrated. To account for these cases, the hypothesis of coronary spasm as the cause of angina was developed. It is now possible to show that most, practically all, patients with angina pectoris do have a diminished blood supply to the heart, since practically all patients with angina have either coronary disease or aortic insufficiency. In the one case the decreased flow is due to anatomic alterations in the coronary vessels; in the other it is due to physiologic changes resulting from the valvular lesion. The end-result in both conditions is the same: anoxemia of the myocardium. It is no longer necessary to assume that spasm of the coronaries takes place in angina, a hypothesis which rests on uncertain evidence and to which there are weighty objections.

The relative frequency of angina pectoris in cases of aortic insufficiency caused by syphilis as compared with the occurrence of angina in cases of rheumatic aortic insufficiency has been pointed out and should be discussed. We believe that this discrepancy can be explained. In the first place, the valvular disease differs in the two types of cases. In syphilitic aortic insufficiency the valvular lesion is "pure," that is to say, it is uncomplicated by the presence of aortic stenosis. In rheumatic aortic insufficiency, however, there is likely to be associated a more or less marked degree of stenosis, which tends to counterbalance the effects of the insufficiency. The result is that usually the insufficiency is more marked in the syphilitic cases as evidenced by the greater lowering of diastolic blood pressure, the higher pulse pressure, etc. In the second place, and probably of great importance, is the fact that many of the patients with syphilitic aortic insufficiency have, in addition to this lesion, narrowing or complete occlusion of the orifices of one or both coronary arteries. As either one of these lesions may lead to a certain amount of diminution of coronary flow, the combined effect of the two tends to cause a greater disturbance than is likely to occur in the average case of rheumatic aortic insufficiency.

24. Smith, F. M.; Miller, G. H., and Graber, V. C.: The Relative Importance of the Systolic and Diastolic Blood Pressure in Maintaining the Coronary Circulation, Arch. Int. Med. **38**:109 (July) 1926.

Syphilitic Aortitis.—It is well, at this point, to discuss the relationship of syphilitic aortitis to angina pectoris. The frequent association of the two conditions has been considered important evidence in favor of the aortic theory, particularly since aortic involvement seemed to account for the cases not explained by the coronary theory. However, it is essential that the facts of the case be carefully examined. It is insufficient to state merely that syphilitic aortitis was present in a case of angina; it is important to know whether syphilitic aortitis alone existed, or whether this condition was complicated by the presence of other lesions, namely, aortic insufficiency or occlusion of the coronary ostia, so commonly found in syphilitic aortitis. For example, it has been stated by Lamb [14] that angina pectoris occurred in 11.35 per cent of 613 cases of syphilitic aortitis collected from the literature, yet it is difficult to determine from the published data the exact extent of the lesions found at necropsy.

TABLE 3.—*Angina Pectoris in Syphilitic Aortitis: Observations at Necropsies*

Authors	Total	Aortic Insufficiency	Coronary Involvement	Combined Aortic Insufficiency and Coronary Disease
Present series	5	5	2	2
Gallavardin: Les angines de poitrine, ed. 1, Paris, Masson & Cie, 1925	7	3	7	3
Pauli: Ztschr. f. Kreislaufforsch. **19**:169, 1927	6	2	6	2
Curshmann, quoted by Stadler: Die Klinik der Syphilitischen Aortenerkrankung, Jena, Gustav Fischer, 1912	1	..	1	..
Osler: Lancet **1**:697, 839 and 973, 1910; M. Chron. **44**:11, 1906	5	3	3	2
Mackenzie: Angina Pectoris, London, Oxford University Press, 1923	5	3	5	3
Pincoffs: Tr. Am. A. Phys. **42**:54, 1927	10	Not mentioned	6	..
Thayer: Internat. Clin. **1**:1, 1923	9	Not mentioned	5	..

We [25] previously reported twenty-six cases of uncomplicated syphilitic aortitis, proved by necropsy, and in not one instance was there a history of angina pectoris. In table 3, we have listed the information obtained from some of the data in the literature.

In every case in which detailed information is given, either aortic insufficiency or coronary disease, or a combination of the two, is present in cases of angina pectoris associated with syphilitic aortitis. This is apparently true, too, in case of angina associated with aneurism. Frankel [8] called attention to the fact that angina occurred in patients with aneurism, particularly when there were arteriosclerotic changes in the region of the coronary vessels. Mackenzie [12] recorded an instance (case 20) in which the coronaries were sclerosed and stated that "I am therefore of the opinion that, when the pain in such cases (aneurism) is found in the region characteristic of angina, it is the heart trouble

25. Keefer, C. S., and Resnik, W. H.: Paroxysmal Dyspnea as a Symptom of Syphilitic Aortitis, Arch. Int. Med. **37**:264 (Feb.) 1926.

which induces the pain." Similarly, Graham Steele [26] stated that the coronary orifices were always involved in cases of angina associated with aneurism. In the two cases described by Osler [27] in which necropsy notes are available, coronary disease was present in one and aortic insufficiency in the other.

In view of these facts, we are led to the conclusion that uncomplicated syphilitic aortitis never causes angina pectoris. When angina occurs in a case of syphilitic aortitis, either coronary disease or aortic insufficiency is also present.

It is not difficult to understand why aortic involvement is actually present in most cases of angina. Reference to the previously given classification of the pathologic conditions associated with angina pectoris will make this clear. We repeat that practically all cases of angina are associated with either coronary disease or aortic insufficiency. When coronary sclerosis is present, there are practically always sclerotic changes in the aorta. When narrowing of the coronary ostia exists, the condition is actually caused by syphilitic or arteriosclerotic lesions in the aorta. On the other hand, when angina is associated with aortic insufficiency, the insufficiency is caused in most instances by syphilitic aortitis; and it was just the few remaining cases of rheumatic aortic insufficiency, in which aortic lesions are not necessarily found that Allbutt was unable to explain by the aortic theory.[28] We see, therefore, that aortic involvement is purely coincidental in angina. It happens to cause or to be associated frequently with the lesions that are responsible for angina.

Miscellaneous Conditions (Associated with Angina).—Although coronary disease or aortic insufficiency or both are present in almost every instance of angina, there are exceptional cases associated with other conditions. It is true that angina has been reported in a wide

26. Steele, Graham: Intrathoracic Tumors and Aneurysms in their Clinical Aspect, Lancet **2**:1605 (Dec. 9) 1911.

27. Osler, Sir William: Angina Pectoris as an Early Symptom in Aneurism of the Aorta, M. Chron. **44**:11, 1906.

28. We are aware of the recent reports concerning the presence of aortic lesions in acute rheumatic fever (Pappenheimer, A. M., and von Glahn, W. C.: Studies in the Pathology of Rheumatic Fever, Am. J. Path. **3**:583 [Nov.] 1927). However, we do not feel that these observations affect our conclusions. Before one could admit any possible bearing of these lesions on the occurrence of angina in patients with rheumatic heart disease, one would have to show that the lesions were present in every case associated with angina, and that most, if not all, of the patients in whom the lesions were present suffered from angina. In none of the cases described by Pappenheimer and von Glahn was true angina present; nor have the aortic lesions been described in any case of which we are aware of a patient with rheumatic aortic insufficiency associated with angina on whom necropsy was performed.

variety of maladies, but a detailed discussion of all of these instances would be profitless. In many cases, what has been termed angina has not been true angina; in many other cases, accurate pathologic data are lacking or incomplete. Thus, angina has been reported in cases of myxedema (Osler,[9] Means, White and Krantz [29] and Sturgis.[30] In one case studied by Sturgis, there was a severe secondary anemia, and necropsy showed extensive coronary changes. It is difficult under these circumstances to estimate accurately the rôle of the hypothyroidism or of the subsequent influence of thyroid extract, although it is possible to speculate on the effect of increasing the circulatory minute volume and the work of the heart by increasing the metabolism. Cases of angina have been described in association with hyperthyroidism (Means, White and Krantz,[29] Sturgis [30] and Chvostek.[31] We, too, have seen a patient whose attacks of angina pectoris were closely related to periods of active hyperthyroidism. During remissions, the attacks disappeared. But the condition of the coronary arteries is unknown in all these cases, and further discussion should be deferred until more definite and complete information is obtained. The same must be said about the attacks of pain that sometimes occur in paroxysmal tachycardia (Mackenzie,[12] Gallavardin [10] and Barnes and Willius.[32] Here, again, it is interesting to speculate on the part played by changes in coronary circulation and in work of the heart (demand for oxygen), but the question must be left undecided until we have further evidence regarding the anatomic state of the coronary arteries, and the alterations in coronary flow. It should be emphasized that it is essential to differentiate between the patients who have paroxysmal tachycardia as a result of coronary occlusion and those who develop angina because of the tachycardia. Angina has also been found in cases of Addison's disease (Rowntree [33]) and polycythemia vera (Kahn [34]), but necropsy records are not available.

There are certain cases, however, from which one may draw more definite conclusions, and they are of considerable interest.

---

29. Means, J. C.; White, P. D., and Krantz, I. C.: Observations on the Heart in Myxedema with Special Reference to Dilatation and Angina Pectoris, Boston M. & S. J. **195**:455, 1926.

30. Sturgis, C. C.: Angina Pectoris as a Complication in Myxedema and Exophthalmic Goitre, Boston M. & S. J. **195**:351, 1925.

31. Chvostek, F.: Morbus Basedowi und die Hyperthyreosen, Berlin, Julius Springer, 1917, p. 73.

32. Barnes, A. R., and Willius, F. A.: Cardiac Pain in Paroxysmal Tachycardia, Am. Heart J. **2**:490 (June) 1927.

33. Rowntree, L.: Studies in Addison's Disease, Tr. A. Am. Phys. **39**:426, 1924.

34. Kahn, M. H.: Etiologic Factors in Angina Pectoris, Am. J. M. Sc., **172**: 195 (Aug.) 1926.

Anemia: Herrick and Nuzum [22] made the important observation that angina is sometimes associated with anemia. Later, Herrick [35] recorded additional cases and collected the literature on the subject. Coombs [36] and Bullrich [37] made similar observations, and the cases may be discussed together. It was found that the severity of the angina was proportional to the degree of the anemia; as the condition of the blood improved the angina tended to disappear. In the few patients on whom necropsy was performed, sclerotic changes were found in the coronary arteries, and Bullrich suggested that the anemia acted by diminishing the nutrition of the myocardium, already impaired by coronary disease. Mackenzie,[12] Levine,[38] Conner [39] and we have also observed cases in which there appeared to be a definite connection between the severity of anemia and the onset of attacks of angina pectoris.

Another important contribution was made by Willius and Giffin [40] who recently reported a case of pernicious anemia with typical attacks of angina. At necropsy, the coronary vessels and the aorta were found to be normal. Cabot [41] also briefly mentioned three similar cases.

Though these cases are few in number, they are of great importance since they demonstrate beyond question the rôle of diminished oxygen supply to the heart in causing angina pectoris.

Arteriovenous Fistula: Attacks of angina have been described in a few instances of arteriovenous fistula, the angina disappearing following surgical closure of the fistula (Perthes [42]). This observation is of interest in view of the work of Lewis and Drury,[23] and of Smith, Miller and Graber,[24] who showed that in arteriovenous fistula a lowering of the diastolic blood pressure and a consequent diminution in coronary flow result. This work adds significance to the report of Osler [43] that sudden death has occurred in patients with arteriovenous fistula, no obvious cause being found at necropsy.

---

35. Herrick, J. B.: On the Combination of Angina Pectoris and Severe Anemia, Am. Heart J. **2**:351 (April) 1927; also, Tr. A. Am. Phys. **42**:23, 1927.

36. Coombs, C. F.: A Note on the Cardiac Symptoms of Pernicious Anemia, Brit. M. J. **1**:185, 1926.

37. Bullrich, R. A.: Influencia patogenica de los estados anemicos sobre la angina de pecho, Semana méd. **2**:1137, 1925, quoted from Herrick; Am. Heart J. **2**:351, 1927.

38. Levine, S. A.: Discussion, Tr. A. Am. Phys. **42**:30, 1927.

39. Conner, L. A.: Discussion, Tr. A. Am. Phys. **42**:29, 1927.

40. Willius, F. A., and Giffin, H. Z.: The Anginal Syndrome in Pernicious Anemia, Am. J. M. Sc. **174**:30 (July) 1927.

41. Cabot, R. C.: Facts about the Heart, ed. 1, Philadelphia, W. B. Saunders Company, 1926.

42. Perthes, G.: München. med. Wchnschr. **32**:1113 (Aug. 8) 1924.

43. Osler, Sir William: Remarks on Arterio-Venous Aneurysm, Lancet **1**:949, 1915.

Pericarditis: We shall discuss the question of pericarditis and angina pectoris, not because of any intrinsic interest in the subject, but because of certain significance that has been attached to it. Pawinski [44] described several cases of angina occurring in patients with pericarditis, and Allbutt referred to this paper in support of his view that the pain in coronary occlusion was due to the development of pericarditis. However, Pawinski's paper was written at a time when the clinical picture of acute coronary obstruction was not well recognized. While but few necropsy data are given in the report, it seems clear from the clinical description and course of five cases, that the diagnosis of coronary occlusion is highly probable. In other words, pericarditis was the result of the angina (coronary occlusion) and not the cause. Moreover, in three other cases, aortic insufficiency was present and the part played by the pericarditis in causing the angina is again rendered doubtful. We do not know of any cases in which the dependence of angina on pericarditis is beyond question.

Neusser [7] stated that attacks of angina pectoris had been reported in a few patients with adherent pericardium. In some of these, pericardial adhesions had caused constriction of the coronary arteries; in others, however, the coronary arteries were apparently intact. But he did not give any further data about the presence or absence of other lesions, such as valvular disease, without which the cases neither support nor refute the anoxemia theory.

Mitral Stenosis: The infrequency of angina pectoris in patients with mitral stenosis has long been recognized, although rare cases have been reported (Levine,[17] Mackenzie [12] and Nothnagel [6]). In some cases, necropsy was not performed; in others, aortic insufficiency or coronary disease was present, rendering the significance of the mitral disease doubtful. Sternberg [45] reported a case of interest. He found at necropsy that the left anterior descending coronary artery may be compressed between the left auricle and the pulmonary artery in certain cases of mitral stenosis. In view of this observation, he suggested that this obstruction of coronary flow might be the cause of anginal attacks in cases of mitral stenosis. Telia [46] offered a similar explanation in an apparently identical case. It is difficult to understand, however, how the coronary artery, under arterial pressure, could be seriously compromised

44. Pawinski, J.: Ueber den Einfluss der trockenen Pericarditis auf die Entstehung der Stenocardie und cardial Asthma, Deutsches Arch. f. klin. Med. **58**:565, 1896-1897.

45. Sternberg, M.: Stenokardie bei Mitralfehlern, Ztschr. f. klin. Med. **97**: 110, 1923.

46. Telia, L.: Considerations sur le syndrome de l'angine de poitrine dans la stenose mitrale, Arch. d mal. du coeur **18**:531, 1925; abstr., Am. Heart J. **1**:386, 1926.

by pressure between structures ordinarily under considerably less tension. Without more data, it must be confessed that the validity of the explanation given is open to question.

There remain but few cases which may be considered possible examples of genuine angina pectoris and which do not fall into one of the groups described. Osler's case,[9] in which lesions of the coronary arteries or aorta were absent, is open to question. One is impressed by the atypical features of the attacks of pain, and the relationship of the final attack to the death is doubtful, as chloroform had been administered during the attack. It has been demonstrated by Levy [47] that this substance is capable of causing sudden death by inducing ventricular fibrillation. Of all Gallavardin's patients in whom genuine angina was considered to be present, only one failed to show coronary disease or aortic insufficiency at necropsy. In this instance, "azotemic" nephritis was present, a condition frequently associated with severe anemia. It is not stated whether anemia was present in this patient; but without this information it is impossible to be certain that anoxemia of the heart was not present. Allbutt [3] was able to collect but fifteen cases from the literature. However, one (case 13) was clearly an instance of coronary obstruction, and in four aortic insufficiency was present. In the others, the condition of the aortic valves or anemia are not mentioned. It is not only impossible to exclude anoxemia in some of these cases, but it is possible that the cases were not instances of genuine angina pectoris, but belonged rather to the group described by Gallavardin [10] as being "para-dyspnoeic," and which he considers distinct from genuine angina.

In summarizing this section on the pathology of angina pectoris, we feel justified in stating that when the facts are complete, it is possible to demonstrate conditions capable of leading to anoxemia of the myocardium in practically every case. In the few remaining cases in which this is not apparently true, either the diagnosis is doubtful or the data are inadequate to exclude the possibility of anoxemia being present.

CRITICAL REVIEW OF PREVAILING THEORIES OF PATHOGENESIS OF ANGINA PECTORIS

There are, at present, three outstanding theories of the pathogenesis of angina pectoris which merit particular attention: (1) coronary theory; (2) aortic theory; (3) myocardial exhaustion theory.

1. *Disease of the Coronary Arteries.*—It was natural that coronary disease should have been implicated early in the explanation of the mechanism of angina pectoris. Coronary obstruction, more or less complete, either by a sclerotic process in the course of the artery, or by

47. Levy, A. G.: The Exciting Causes of Ventricular Fibrillation in Animals Under Chloroform Anesthesia, Heart **4**:319, 1912-1913.

occlusion of the mouth of a coronary artery through sclerosis or syphilitic involvement of the aorta, was so frequently found at autopsy in persons with the condition, that a connection seemed inevitable. This view, first proposed by Jenner and Parry, and later brilliantly upheld by Potain and Huchard, has, nevertheless, been abandoned in its strict sense. Two important obstacles stood in the way of accepting this theory: (*a*) cases in which marked obstruction of the coronary arteries was found, in which angina pectoris had not been present during life, (*b*) cases of unquestionable angina pectoris in which the coronary arteries were found absolutely uninvolved at autopsy.

The first objection to the coronary theory, namely, that coronary obstruction can exist without angina pectoris being present, can no longer be considered valid. This objection was raised at a time when it was held that the coronary arteries were terminal arteries and did not have any appreciable anastomotic relationship with each other. Modern work has shown that this assumption is untrue. The work of Gross,[48] Spalteholz [49] and Oberhelman and LeCount [50] has demonstrated beyond a doubt that relatively rich communications may exist between the branches of the coronaries, the extent of the anastomosis usually increasing with the age of the patient. Moreover, it is a matter of common observation that particularly in syphilitic involvement of the aorta, the mouth of a coronary artery may be completely occluded without any evidence of myocardial infarction; that is to say without any evidence to show that the heart muscle supplied by the occluded artery had suffered any nutritional disturbance. These observations led to the view (Oberhelman and LeCount [50]) that myocardial damage depends on: (*a*) the rapidity with which the occlusion takes place—the slower the process the greater the opportunity for anastomosis to develop; (*b*) the richness of the preexistent anastomosis with the obstructed vessel. Even in the event of an acute obstruction, the connections with the occluded vessel may be so extensive that a serious diminution in the supply of blood to the area of the heart muscle supplied by the obstructed vessel need not develop. The recent work of Wearn [51] has emphasized the importance of another avenue by which the myocardium may receive an adequate blood supply in spite of a coronary obstruction, namely, the Thebesian vessels.

48. Gross, L.: The Blood Supply to the Heart, in Its Anatomical and Clinical Aspects, ed. 1, New York, Paul B. Hoeber, 1921.

49. Spalteholz, W.: Die Arterien der Herzwand, Leipzig, 1924.

50. Oberhelman, H. A., and LeCount, E. R.: Variations in Anastomosis of Coronary Arteries and their Sequences, J. A. M. A. **82**:1321 (April 26) 1924.

51. Wearn, J. T.: The Rôle of the Thebesian Vessels in the Circulation of the Heart, J. Exper. Med. **47**:293 (Feb. 1) 1928.

Another important factor of a different nature must be considered; namely, the sensitivity of the patient to pain (Libman [52]). There is a condition in which association with pain is unquestioned, namely, acute coronary obstruction with myocardial infarction. Yet even in this condition there may be a complete absence of pain. It is not uncommon to find at autopsy old scars in the heart muscle, or even fresher infarcts, due to coronary obstruction in cases in which a history of pain was not elicited.[53] Huchard [4] and Gallavardin [10] reported such instances, and attributed the absence of pain to the fact that pain could not arise from dead tissue. We do not consider this explanation satisfactory. Pain cannot be expected to arise from dead tissue; but this tissue must first pass through a stage of injury, when one does expect pain. There can be but little doubt that it is the injury of the myocardium and not the actual death, that causes pain in cases in which there is a myocardial infarct. We are more inclined to feel that in these instances of myocardial infarct pain is absent (*a*) either because the subject is relatively insensitive to pain;[54] (*b*) or because the infarction occurs so slowly, only a few fibers being injured at a time, that the resulting sensation is insufficient to arise in consciousness. These cases are different from those (Herrick [55]) in which following the obstruction with its accompanying pain, the angina disappears. Here it is logical to assume that the infarction and subsequent scarring has thrown out of function, beyond doubt, the area of myocardium previously responsible for the pain.

In view of the foregoing two considerations (*a*) instances in which adequate blood supply to the occluded territory is assured by compensatory anastomosis between the coronary arteries and further by the Thebesian vessels so that infarction does not take place, and (*b*)

52. Libman, E.: Observations on Sensitiveness to Pain, Tr. A. Am. Phys. **41**: 305, 1926.

53. We are unable to account for Gallavardin's (footnote 10) statement that in twenty-two of twenty-five cases of coronary obstruction with infarction, pain was not present. These figures give a totally different impression from those published in papers coming from this country. (Herrick, J. B.: Acute Obstruction of the Coronary Artery, Northwest Med. **24**:593 [Dec. 25] 1925; Clinical Features of Sudden Obstruction of the Coronary Arteries, J. A. M. A. **59**:2015 [Dec. 7] 1912; Thrombosis of the Coronary Arteries, ibid. **72**:387 [Feb. 8] 1919. Wearn, J. T.: Thrombosis of the Coronary Arteries with Infarction of the Heart, Am. J. M. Sc. **165**:250 [Feb.] 1923. Libman, E.: Some Observations on Thrombosis of the Coronary Arteries, Tr. A. Am. Phys. **34**:138, 1919. Hamman, L. V.: The Symptoms of Coronary Occlusion, Bull. Johns Hopkins Hosp. **38**:273 [April] 1926.)

54. This view is not far-fetched. One is not astonished at observing a fatal hemorrhage or perforation from a large peptic ulcer which had hitherto remained absolutely symptomless, or which may be discovered as an unsuspected observation at autopsy.

55. Herrick (footnote 53, first reference).

instances in which pain is probably not felt even when infarction does ensue, either because of the patient's diminished sensitivity to pain, or because of the slowness of the process of infarction, it can no longer be held that coronary disease without angina pectoris is a valid argument against the theory that the coronary arteries are implicated in angina pectoris.

There remain the cases of angina pectoris without organic coronary disease. These cases constitute a far more serious objection to the acceptance of an exclusive coronary theory. Albutt enumerated fifteen, and there are others in the literature. Some of these cases are unquestionably instances of genuine angina; but there is serious doubt about the accuracy of the diagnosis in others. For example, Neusser [56] cited a case of Heine, one of so-called "plexus angina," in which at autopsy lesions (apparently, tuberculous lymph nodes) were found involving the phrenic and cardiac nerves and branches of the left vagus nerves. However, Neusser [7] himself admitted that the clinical history was not typical of angina pectoris, as there was no characteristic pain on effort. It seems more likely that transient complete heart block was present. Neusser [57] also quoted a case of Wallenberg, in which, following a stab wound, there was "anguish in the cardiac region," together with a sensation as if the heart "stood still." Here again the history of the attacks is altogether atypical, and the diagnosis of angina pectoris is scarcely permissible. These cases are illustrative of many that have been inaccurately included under the category of angina pectoris merely because the patient has experienced distress in the region of the heart. They have served only to confuse the problem. It would be impossible to cover the entire literature of angina pectoris in an effort to sort out the cases of true angina from those in which the diagnosis is more or less questionable. One must agree with Gallavardin [58] that "angina pectoris without coronary lesions does not mean much, if one does not definite precisely with which syndrome one deals."

Aside from the cases in which the history is sufficiently atypical that one has adequate grounds on which to question the accuracy of the diagnosis of angina pectoris, there are other examples in which it must be admitted that a close similarity with undoubted angina exists. We have shown, however, that practically all the patients have aortic insufficiency or some other lesion that may produce anoxemia of the myocardium.

---

56. Von Neusser, E.: Angina Pectoris, New York, E. B. Treat & Co., 1909, p. 35, trans. into English by Andrew MacFarlane.

57. Von Neusser, E.: Angina Pectoris, New York, E. B. Treat & Co., 1909, p. 41, trans. into English by Andrew MacFarlane.

58. Gallavardin, L.: Les angines de poitrine, ed. 1, Paris, Masson & Cie., 1925, p. 128.

The coronary theory has been powerfully supported by the better appreciation of the clinical picture of acute coronary occlusion. This condition is so similar in many important respects to angina pectoris that a connection between the two has seemed unavoidable to many students of the subject. It is true that there are differences, which we shall analyze later; but the close correspondence in the essential features is inescapable. Allbutt [3] has objected to this view, one of the reasons being that pain in coronary occlusion is due to the pericarditis that is sometimes associated with the condition; in other words, the pain has an altogether different origin from the pain of angina pectoris. This argument certainly has no basis. Aside from the fact that the type of pain is practically identical with the pain of angina pectoris, and quite different from the pain that one usually encounters in other forms of pericarditis, one needs only to point out that pericarditis is not at all a constant observation in cases of coronary occlusion with pain. For example, Wearn [59] found pericarditis in six of nineteen patients on whom autopsy was performed; of these, fifteen had acute coronary occlusion with pain as an outstanding symptom.

In spite of the objections that have been raised against the theory that organic disease of the coronary arteries (obstruction either in the course of the artery or at the mouth) is responsible for angina pectoris, the idea of coronary involvement has not been abandoned. To account for the cases of angina without coronary disease, the conception of spasmodic constriction of the coronary arteries was evolved. This view, first advocated by Latham [60] and supported by Neusser [7] and many others, among whom may be mentioned Gallavardin [10] and Kohn,[61] seems at first sight to be attractive. The attacks that characterize the condition are spasmodic; in the typical case they occur suddenly, they usually disappear quickly, and the agents that relieve the attacks, the nitrites for example, are those whose action diminishes vascular tone. However, there are difficulties in the way of acceptance of the hypothesis of "coronary spasm."

First of all, it is difficult to understand why this hypothetic spasm of the coronary arteries should occur only in certain types of cases; why, for example, it is excessively rare in rheumatic heart disease, particularly mitral stenosis, and, indeed, in all other types of heart disease except those associated with coronary disease or syphilitic aortitis. Secondly, it is difficult to understand how vasoconstriction could affect a coronary artery which was already altered by arterio-

59. Wearn (footnote 53).

60. Latham, P. M.: Diseases of the Heart, London, 1845, quoted from Kohn, H.: Med. Klin. **22**:983, 1026 and 1063, 1926.

61. Kohn, H.: Angina Pectoris, Aorten oder Koronarhypothese, Med. Klin. **22**:983 (June 25) 1926; **22**:1026 (July 2) 1926; **22**:1063 (July 9) 1926.

sclerosis. Recognizing that vasoconstriction in an artery thickened and hardened by deposits of lime was a physiologic impossibility, Neusser [7] proposed the idea that angina occurred only when the coronary arteries were slightly or moderately affected; when vasoconstriction could no longer take place, the attacks disappeared. This conception is purely hypothetic, as there is no way of determining in life the degree of sclerosis of the coronary arteries and the possibility of vasoconstriction. Moreover, it is contrary to experience, at least in the majority of cases, since one finds at autopsy more often than not a high grade of sclerosis in patients who, in life, had suffered from typical attacks of angina up to the time of death. Case 6 of Gallavardin's series [62] may be cited as a single example: "the changes in the coronaries, atheromatous in nature . . . involve the entire extent of the vessels, which, even at the periphery, roll under the finger like little calcified tubes." In the face of the foregoing observations, Gallavardin [63] went so far as to state that in acute coronary obstruction, the pain is not due to the actual obstruction, but rather to the coronary spasm that (he assumes) accompanies it. Yet the symptomatology of acute coronary obstruction may occur in patients in whom at autopsy the coronary arteries do not differ much from those just described. It is, moreover, exceedingly difficult to conceive of a spasm lasting for hours or even days, as does the pain in some cases of coronary obstruction, a spasm which is practically always unaffected by agents that are usually effective. Finally, and most important, the idea of coronary spasm has been proposed and maintained in spite of almost directly contradictory facts of physiology. It has yet to be proved that an effective coronary spasm can actually take place. There has been little support for such an idea from experiments on mammals. Recently, Anrep and Segall [64] have shown in experiments on the heart and lungs that the coronary arteries are actually affected by vasomotor nerves, the sympathetic nerves causing a dilatation, and the vagi, constriction. Even their work has been questioned by Miller, Smith and Graber [65] who were led by their own experiments to the conclusion that diminution of coronary flow on stimulation of the vagi was purely the result of lowering of the heart rate. A final decision must be held in abeyance. If, however, for the sake of argu-

62. Gallavardin, L.: Les angines de poitrine, ed. 1, Paris, Masson & Cie., 1925, p. 143.

63. Gallavardin, L.: Les angines de poitrine, ed. 1, Paris, Masson & Cie., 1925, p. 126.

64. Anrep, G. V., and Segall, H. N.: The Regulation of the Coronary Circulation, Heart **13**:239 (Sept.) 1926.

65. Miller, H. G.; Smith, F. M., and Graber, V. C.: The Influence of Changes in the Cardiac Rate and Irregular Action of the Heart on the Coronary Circulation, Am. Heart J. **2**:479 (June) 1927.

ment, one does assume the possibility of vasoconstriction through stimulation of the vagi, but little support is given the coronary spasm theory in angina pectoris. Anrep and Segall [64] have shown that when the vagus is stimulated, slowing of the heart and diminution of coronary flow do not go hand in hand. When mild stimulation of the vagus is employed, slowing of the heart may occur without any decrease in coronary flow (that is, without vasoconstriction). The clinical application of their important results is that if vasoconstriction does take place, a slowing of the heart rate must be present. The assumption of vasoconstriction in angina pectoris falls to the ground, then, since there are not any characteristic changes in the heart rate during an attack of angina. The rate is usually unaltered; sometimes it is slightly decreased, and sometimes it is slightly increased. But there is no constant decrease, which is a necessary prerequisite for the acceptance of diminished coronary flow due to vagal stimulation, whether Anrep and Segall, or Miller, Smith and Graber be ultimately proved correct. There remains, of course, the possibility that the results of the animal experiments do not necessarily apply to conditions in the human. For the present this is a gratuitous assumption. Together with the other facts at hand, these experimental results remain a most serious obstacle to the idea of coronary spasm in angina pectoris.

One would expect, if coronary spasm were the actual cause of angina pectoris, to find fairly frequent examples of myocardial infarct without organic obstruction of the coronary arteries. Occasionally one does see examples of healed infarct in which complete obstruction of the corresponding branch of the coronary artery does not exist. But these cases can be logically explained on the basis of recanalization of the previously existent thrombus. In addition, one may see areas of patchy necrosis in an area of muscle supplied by a markedly sclerotic coronary artery, which is, however, patent (e, g., cases 4, 6 and 8 of Gallavardin's series). This necrosis is, in all likelihood, due to the gradual death of small groups of muscle fibers caused by impaired coronary flow, rather than to sudden death resulting from complete obstruction. Gruber and Lanz [66] reported a case of infarct of the heart in a young soldier who had, in life, suffered from epileptiform attacks. The coronary arteries were apparently normal and there was not any obvious obstruction. The infarct was thought to be due to coronary spasm, and the epileptiform attacks to spasm of the cerebral vessels. Although the clinical history was not that of angina pectoris, the observations at autopsy apparently support the idea of coronary spasm. However, we do not feel that we

66. Gruber, G. B., and Lanz, H. F.: Ischamsiche Herzmuskelnekrose bei einem Epilepticker nach Tod im Anfall, Arch. f. Psychiat. **61**:98 (Sept.) 1919-1920.

are too conservative when we suggest that such a conclusion be accepted with the greatest caution. If coronary spasm can give rise to the development of myocardial infarct, it becomes surprising that such cases are not more frequent. Yet they must be of the greatest rarity—so rare that one cannot help entertaining a certain degree of skepticism concerning them, particularly when one recalls the admonition of Benson [67] that the arterial occlusion may be overlooked unless special care is used in opening the coronaries.

A modification of the coronary theory has been suggested by Danielopolu,[68] who considers angina to be due to disproportion between coronary flow and work of the heart. That is to say, coronary insufficiency may lead to angina pectoris in a normal heart with normal coronary arteries, if the demands on the heart are great enough; correspondingly lesser demands will bring on angina when the coronary arteries are diseased. Even this author invokes spasm as an explanation of angina under some circumstances. This view is satisfactory as an explanation of the cases with actual coronary disease; however, Danielopolu does not offer convincing evidence that such a coronary insufficiency is present when the coronary arteries are normal.

We may summarize this discussion by stating that, in spite of extensive pathologic evidence, it is not possible to accept a theory which maintains that organic coronary disease is present in every case of angina pectoris. Nor is it possible to accept, without serious question, the hypothesis of vasoconstriction to explain those cases of angina without coronary obstruction.

2. Disease of the Aorta.—This theory is usually identified with the names of Allbutt and Vaquez, and more recently of Wenkebach also. Its chief support rests on the finding of involvement of the aorta in practically all cases of angina pectoris. This comes from the fact that practically all patients with angina have either arteriosclerosis or syphilitic aortitis. But the arguments that have been directed against the coronary theory are applicable to the aortic theory as well: (*a*) There are cases of angina pectoris without demonstrable disease of the aorta. Allbutt himself confessed that he was puzzled by the cases of aortic insufficiency of rheumatic origin in which disease of the aorta could not be discerned. Jamison and Hauser [69] reported a case of angina in a boy of 18 years; the autopsy revealed coronary disease but

67. Benson, R. L.: The Present Status of Coronary Arterial Disease, Arch. Path. **2**:876 (Dec.) 1926.

68. Danielopolu, D.: The Pathology and Surgical Treatment of Angina Pectoris, Brit. M. J. **2**:553 (Sept. 27) 1924.

69. Jamison, S. C., and Hauser, G. H.: Angina Pectoris in a Youth of Eighteen, J. A. M. A. **85**:1389 (Oct. 31) 1925.

no involvement of the aorta. (*b*) Extensive disease of the aorta may be present without the occurrence of angina. One need only think of the frequency of aneurisms in this region, and the comparative rarity of association of angina pectoris. We call attention to a previous study [25] in which a series of twenty-six patients with uncomplicated cases of syphilitic aortitis (proved by autopsy) were found to have been free from both paroxysmal dyspnea and angina pectoris.

To us the most serious objection to the aortic theory is that it does not supply an adequate explanation for the sudden death. It is remarkable that comparatively little attention has been paid to this striking deficiency in the theory. It is true that "vagal inhibition" was proposed by Allbutt as the cause of death in a paroxysm of pain. This explanation may have appeared logical at the time it was first suggested; it can no longer be accepted without grave doubt. Lewis [70] has justly stated: "to accuse the vagus when unexpected syncope terminates life, in the absence of clear evidence of its responsibility is unjustifiable."

If one starts with the assumption that the train of symptoms in angina pectoris, which frequently ends in sudden death, is inaugurated by stimulation of the nerve endings in the aorta, then sudden death can occur only as a result of reflex stimulation through the vagus or sympathetic nerves. We are not aware of any evidence that stimulation of the sympathetic nerves may cause sudden death. The proved cases of standstill of the whole heart caused by vagal stimulation are rare,[71] and the instances in which ventricular standstill has occurred have been almost entirely in cases with some degree of preexistent block. This is certainly not true in most cases of angina pectoris. One may also ask why there are not any evidences of vagal stimulation during severe attacks of angina that do not lead to sudden death. One would expect to find in these cases definite slowing of the heart rate and probably varying degrees of auriculoventricular block, which is not the case. If one asks further why involvement of the aorta without cardiac damage (the coronary arteries being intact and no aortic insufficiency being present) is not associated with sudden death, the answer is given that sudden death depends on the condition of the heart; a healthy heart withstands the vagal attack. If, however, the question depends purely on the condition of the myocardium, it is strange that sudden death is of the utmost rarity in a combination such as syphilitic aortitis and mitral stenosis, for example, even when the heart shows signs of being seriously damaged. In the study previously mentioned [25] we did not find cases of sudden death in instances of syphilitic aortitis associated

70. Lewis, Sir T.: The Mechanism and Graphic Registration of the Heart Beat, ed. 3, London, Shaw & Sons, Ltd., 1925, p. 433.

71. Lewis, Sir T.: The Mechanism and Graphic Registration of the Heart Beat, ed. 3, London, Shaw & Sons, Ltd., 1925, p. 418.

with hypertension and myocardial failure. Finally, as we shall show later, the best evidence points to the sudden death being due to ventricular fibrillation. So far as we know, vagal stimulation does not play an important part in the production of ventricular fibrillation. Experimentally, Drury [72] was not able to detect any influence of vagal stimulation on the refractory period of the ventricle. If, as seems likely, ventricular fibrillation depends on the same mechanism as does auricular fibrillation, namely, the development of a circus movement, it is practically essential that changes in the refractory period of the muscle occur.

In the face of these facts, we cannot see any reason for attributing angina not only exclusively, but even occasionally, to lesions of the aorta. The aortic theory leaves unexplained the cases in which disease of the aorta cannot be discovered; it does not afford a logical explanation for the mechanism of sudden death which is so closely bound with the entire problem of angina; and it rests solely on the fact that most cases of angina are found to have lesions of the aorta, which, we have shown, is purely a coincidence.

3. *Exhaustion of the Myocardium.*—Of Mackenzie's twenty-two patients on whom autopsy was performed, eighteen had definite involvement of the coronary arteries; of these, three had an associated aortic insufficiency, two had aortic stenosis and one had an aneurysm. Two had myocardial changes (presumably due to coronary disease although this is not definitely stated) and two had combined aortic, mitral and tricuspid disease of rheumatic origin. In the latter two patients there apparently was not any coronary disease. Mackenzie was convinced of the importance of the coronary arteries in angina pectoris; but being unable to explain the cases in which the coronaries were uninvolved, he resorted to the conception of "myocardial exhaustion," usually due to deficient blood supply, occasionally to exhaustion from other causes. He confessed that he was puzzled by the frequency of angina pectoris in cases of aortic insufficiency.

One gathers the impression that Mackenzie was essentially a "coronarian" and that the idea of "myocardial exhaustion" was one which was designed to cover those cases in which there was not any coronary disease. In view of the indefiniteness of the term "exhaustion," it is rather difficult to advance arguments for or against this hypothesis. It is not acceptable, however, for it leaves unexplained the irregularity in the occurrence of angina pectoris in various types of heart disease with exhausted heart muscle. It does not account for the frequency of

72. Drury, A. N.: The Influence of Vagal Stimulation upon the Force of Contraction and the Refractory Period of the Ventricular Muscle in the Dog's Heart, Heart **10**:405 (Oct. 23) 1923.

angina in cases with coronary disease or aortic insufficiency or the rarity in cases with mitral stenosis, for example. Indeed, it is well known that when the myocardium is most exhausted, that is, when the evidences of congestive failure are most marked, the symptoms of angina tend to disappear, even in persons who have previously been subject to the condition. It is rather when the myocardium has a relatively good reserve, as manifested by the freedom from dyspnea, that the anginal symptoms are most striking. The hypothesis does not explain why all patients who ultimately die of heart failure, exhaustion of the myocardium, do not sometime in their career, suffer from angina.

In summary, it may be stated that all three of the theories as they stand today are inadequate. On the other hand, we have demonstrated before that practically all cases of "true" angina pectoris have lesions that may produce anoxemia of the myocardium, and it remains to show how anoxemia may bring about the manifestations that characterize angina pectoris.

CAUSE OF PAIN IN ANGINA PECTORIS

The striking similarity between angina pectoris and intermittent claudication has long been noted. In both instances the pain is brought on by effort, it is cramplike in character and rapidly relieved by rest. In intermittent claudication there is not any question about the cause of the pain: it is due to diminished blood supply to the muscles.

The experimental work of MacWilliam and Webster [73] is important in explaining certain characteristics of the pain in skeletal muscle. They found that when the blood supply to the arm is shut off by constriction, pain is not caused even at the end of twenty minutes, provided the muscles remain quiet. When, however, the ischemic arm is made to contract, fatigue is brought on much more quickly than it is in the normal arm, and at the fatigue point, there is severe pain. Moreover, pain can be elicited even before the fatigue point is reached, at a time when the contractile power of the muscle is still good. This latter fact is of importance, since it is at least a partial answer to the objection that may be raised, namely, that heart muscle cannot be fatigued. It demonstrates that whether or not there is any relationship between pain and fatigue under the circumstances of a muscle contracting when its oxygen supply is inadequate, pain is the earlier manifestation. In view of the close correspondence of these results with the clinical facts of angina pectoris, these authors suggest that processes of essentially the same nature are responsible for the pain in the latter condition.

---

73. MacWilliam, J. A., and Webster, W. J.: Some Application of Physiology to Medicine: I. Sensory Phenomena Associated with Defective Blood Supply to Working Muscles, Brit. M. J. **1**:51 (Jan. 13) 1923.

Even more convincing evidence is afforded by the natural experiment of acute coronary obstruction, a condition characterized by one outstanding circumstance, the production of a sudden acute anoxemia of the myocardium. It is scarcely necessary to call attention to the similarity of this pain to that of angina pectoris, attested from the fact that acute coronary occlusion was long called status anginosus. Whatever difference exists between the two conditions is explainable by the persistence of anoxemia in acute coronary obstruction. This condition bears the same relation to angina pectoris that an acute and complete obstruction of the femoral artery bears to intermittent claudication.

Unfortunately, the nature of the problem makes it impossible at present to obtain more direct evidence with regard to the question of pain by means of controlled experiments. When one considers, however, that a picture analogous to that of angina pectoris is produced in skeletal muscle by a diminished blood supply; and also that "status anginosus" is caused clinically by acute coronary obstruction, it seems to us that the evidence is strong that anoxemia of the heart muscle can cause the pain of angina pectoris. This conclusion attains added significance in view of the pathologic data demonstrating in practically every authentic case of angina a lesion that gives rise to anoxemia of the myocardium. Not only, then do we have a highly suggestive and reasonable explanation for the pain in angina but we are not aware of any actual facts that speak so directly for distention of a diseased aorta as a possible cause of anginal pain. One would expect such a pain to arise in many instances of tabetic crises, for example, or in attacks of lead colic, in which a sudden acute hypertension occurs, presumably causing at least as much distention of the aortic wall as will occur in the ordinary muscular exercise that brings on pain in angina pectoris. This is not the case. Nor is there any actual support for the belief that an "exhausted" myocardium can cause pain which simulates closely the pain of angina.

It would not serve any useful purpose to speculate much on the actual mechanism of pain stimulation in the presence of anoxemia of the myocardium. Nor is it pertinent to this discussion to comment on the nervous pathways of the sensory stimuli from the heart. It is well to call to mind again, however, a point which we have already mentioned, namely, the probable variation in sensitivity to pain in different persons, as this may account for the occurrence of marked coronary disease, even with complete obstruction, in patients who may ultimately die of the disease, without ever having experienced pain during life.

CAUSE OF SUDDEN DEATH IN ANGINA PECTORIS

One of the remarkable features of angina pectoris is the frequency of sudden death. This has been commented on since the time of Heberden. Of Mackenzie's 284 fatal cases, 120 terminated suddenly.

As the figure 284 includes many instances of "secondary" angina, that is to say, cases which were not true angina at all, the percentage of sudden deaths among the cases of true angina is higher than would appear from the figures. In Windler's [74] group of twenty-eight patients, sixteen died suddenly. In a group of twenty-three fatal cases studied by Willius,[75] in eighteen, or 76 per cent, death was sudden. In our own group of fifteen fatal cases, eleven ended by sudden death. It would seem that about 60 to 75 per cent of the patients with angina die suddenly.

It may be well to approach the topic from another angle, and to inquire in what forms of heart disease sudden death comparable to the death in many cases of angina is likely to occur. The frequency in coronary disease is well known. Thus, in 200 patients with more or less extensive coronary disease, 160, or 80 per cent, died suddenly (Benson and Hunter [76]). In another group, 49 per cent of the patients with arteriosclerotic heart disease died suddenly (Willius). It is probable that approximately the same percentage of instances of sudden death would be found in other large series of cases of marked coronary disease. The other condition in which sudden death is a striking occurrence is aortic insufficiency, particularly of syphilitic origin. This is a well known clinical fact. In a group of twenty-one fatal cases of syphilitic aortic insufficiency that we have observed in sixteen, or 76 per cent, death was sudden; of these, in eight there was occlusion of one of the coronary ostia. Stadler [77] reported sudden death in twenty-three of his fifty-two patients with aortic insufficiency; there was encroachment of the coronary orifices in twenty-two instances, a remarkably high percentage. While sudden death may occur when the coronary arteries are involved, it is much more frequent when aortic insufficiency is present as well. Sudden death is not infrequent in rheumatic aortic insufficiency, and Moore [78] stated that "such cases generally terminate in sudden death and, of all causes of transition from what seems fair health to immediate death, aortic valvular disease is the most frequent."

We have not attempted to gather more statistics bearing on this subject, as we believe the conclusions are sufficiently well recognized

74. Windler, quoted by Mackenzie (footnote 12, p. 114).

75. Willius, F. A.: Mode of Death in Various Types of Heart Disease, Am. J. M. Sc. **171**:480, 1926.

76. Benson, R. L., and Hunter, W. C.: The Pathology of Coronary Arterial Disease, Northwest Med. **24**:606 (Dec.) 1925.

77. Stadler, E.: Die Klinik der syphilitischen Aortenerkrankung, Jena, Gustav Fischer, 1912.

78. Moore, Norman: Rheumatic Fever and Valvular Disease, Lancet **1**:1159 (April 24) 1909; **1**:1227 (May 1) 1909; **1**:1297 (May 8) 1909.

to be beyond serious dispute. It is seen then, that sudden death occurs in exactly those conditions with which angina pectoris is most often associated: coronary disease and aortic insufficiency, especially of syphilitic origin. There is apparently some fundamental relationship between the characteristic pain of angina pectoris and the phenomenon of sudden death.

To MacWilliam [79] belongs the credit of having first suggested ventricular fibrillation as the probable mechanism by which sudden death occurs in heart disease. He was led to this conclusion from the observation that in experimental work on animals, sudden death always resulted at the onset of this rhythm; it never took place by sudden standstill of the heart. He also noted that ventricular fibrillation was particularly prone to occur when the ventricles were rendered susceptible by a poor blood supply, or by the long duration of the experiment. Resnik [80] also pointed out the marked tendency for ventricular fibrillation to develop when dogs were subjected to breathing mixtures of low oxygen pressure. Under these conditions, the abnormal rhythm sometimes occurred spontaneously; more frequently it was caused by some stimulus, such as slight handling of the ventricle, a procedure insufficient ordinarily to cause such an effect in a well-oxygenated heart.

Further important experimental evidence is available in the work of Lewis [81] and of Smith [82] on experimental ligation of the coronary arteries. They showed that sudden death following the ligation was due to ventricular fibrillation, often preceded by ventricular tachycardia. In the light of these experiments, considerable significance is attached to the observations of Robinson and Hermann [83] who reported clinical cases of ventricular tachycardia due to coronary occlusion.

When we sum up these data, we find that not only does angina pectoris terminate suddenly in a high percentage of cases, but that sudden death in heart disease occurs in just those cases that have lesions

---

79. MacWilliam, J. A.: Cardiac Failure and Sudden Death, Brit. M. J. **1**:6 (Jan. 5) 1889; Some Applications of Physiology to Medicine: II. Ventricular Fibrillation and Sudden Death, ibid. **2**:215 (Aug. 11) 1923.

80. Resnik, W. H.: Observations on the Effect of Anoxemia on the Heart: I. Auricular Ventricular Conduction, J. Clin. Investigation **2**:93, 1925; II. Intraventricular Conductions, ibid. **2**:117, 1925; III. Changes in the Auricles, with Particular Reference to the Relationship Between Anoxemia and Auricular Fibrillation, ibid. **2**:125, 1925.

81. Lewis, T.: The Experimental Production of Paroxysmal Tachycardia and the Effect of Ligation of the Coronary Arteries, Heart **1**:98, 1908.

82. Smith, F. M.: The Ligation of Coronary Arteries with Electrocardiographic Study, Arch. Int. Med. **22**:8 (July) 1918; Electrocardiographic Changes Following Occlusion of the Left Coronary Artery, ibid. **32**:497 (Oct.) 1923.

83. Robinson, G. C., and Hermann, G.: Paroxysmal Tachycardia of Ventricular Origin and Its Relation to Coronary Occlusion, Heart **8**:59, 1921.

commonly associated with angina. We find also that the weight of experimental evidence supports the view that sudden death is practically always due to ventricular fibrillation, and that this rhythm is particularly likely to develop under conditions that produce anoxemia of the myocardium. Finally, there is proof that ventricular tachycardia, a forerunner of fibrillation, is frequently due to coronary obstruction in clinical cases.

Not uncommonly sudden death occurs in patients who have apparently never suffered pain. We have already referred to the frequency of such an event in patients with syphilitic aortic insufficiency or with more or less severe coronary obstruction. It is reasonable to assume that the state of anoxemia dependent on these lesions has predisposed the ventricles to fibrillation, as it does experimentally. This rhythm may then develop spontaneously, or it may be set off by some stimulus. It is possible that an extrasystole may act in such a manner, just as a properly timed shock may experimentally determine the onset of auricular fibrillation (Lewis). It is, of course, practically impossible to determine with certainty what the actual final stimulus is that causes the appearance of ventricular fibrillation in the clinical case. It would seem, however, that some condition producing anoxemia of the ventricle is an almost necessary predisposing factor.

If we accept the views that anoxemia of the heart muscle produces the pain of angina pectoris, and that ventricular fibrillation, caused fundamentally by anoxemia, is the cause of sudden death, it becomes clear why sudden death is so common in angina and why this frequent outcome is so inseparably bound with true angina. The pain and the sudden death are both expressions of the same underlying cause. One may almost state that the termination of the condition depends on the accidental development of circumstances that favor the appearance of ventricular fibrillation. Once the ventricle has been rendered susceptible by anoxemia, this rhythm may appear at any time, usually after paroxysms of pain have occurred over varying periods, sometimes even before any pain has ever been caused. Its appearance is synonymous with practically instantaneous death.

ANGINA PECTORIS AND CORONARY OBSTRUCTION

We have already intimated that the close similarity between the clinical aspects of angina pectoris and acute coronary occlusion constitutes evidence of great importance in establishing the coronary (anoxemia) theory. Yet the fact that there are certain differences in these conditions has been used by Allbutt [3] to discredit the strength of the argument. Lambert [84] has also emphasized the differences between

84. Lambert, Alexander: Cardiac Pain, Am. Heart J. **2**:18, 1926.

coronary disease and angina pectoris, and they can best be shown by the following outline:

Coronary Disease	*Angina Pectoris*
Epigastric pain more common	Epigastric pain less common
Dyspnea present	Dyspnea absent
Arrhythmias frequent	Arrhythmias absent
Frequency of râles in lungs	Lung signs absent
Pain is of long duration	Pain is of short duration
Nitrites do not give relief	Pain relieved by nitrites
Attacks may occur at night	Attacks rare at night, except late in disease

It is obvious that what is called "coronary disease" by Lambert is actually acute coronary obstruction. That being the case, one may add other differential points: fever, leukocytosis, pericarditis, emboli in distant organs, low blood pressure, acute pulmonary edema and urinary suppression—all these occurring in acute coronary occlusion and all absent in angina pectoris. However, none of these so-called differential points holds in coronary disease without complete occlusion, and it is not difficult to explain their presence when acute and complete occlusion does take place.

The position and radiation of the pain do not differ fundamentally in the two conditions, usually being exactly the same. It does seem true that epigastric pain is relatively more common when acute obstruction develops; but epigastric pain in angina pectoris is far from uncommon, and such a relative difference can hardly be considered of serious import in distinguishing between "coronary disease" and angina pectoris. The occurrence of dyspnea, arrhythmias and signs of congestion in the lungs are simply and logically attributed to the fact that in acute coronary obstruction, myocardial infarction takes place; a greater or lesser part of the myocardium is thrown completely out of function. It is not surprising, under these circumstances, if changes in rhythm and signs of myocardial failure (so-called congestive type) arise. It is characteristic of angina pectoris that when pain develops, the patient stops short and usually maintains absolute quiet until the paroxysm has disappeared. Such absolute quiet is not often present in cases of acute coronary obstruction; and with good reason. The patient with angina is brought to a halt by his pain since he has learned from experience that the less he moves, the more rapidly will his pain disappear. The patient overcome by coronary occlusion is not faced by any such happy solution of his problems. As in typical angina, anoxemia of the myocardium develops. However, it is not due to a transient inability on the part of the heart muscle to receive an adequate supply of oxygen. It is due to a lesion which cuts off the oxygen supply permanently. Not only, then, is the pain more severe, but it persists

The most profound quiet will not cause its underlying cause to disappear. Is it to be wondered at that such a patient does become restless and toss about? This is what will occur in any condition associated with excruciating pain when quiet will not relieve the pain. It becomes apparent, too, why nitrites will not affect such a pain. It does so in angina pectoris by lowering the blood pressure and possibly dilating the coronary arteries, thus doing away with the condition of relative anoxemia of the heart: diminishing the demand for oxygen, and at the same time increasing the supply. These effects can have little or no influence on a type of anoxemia caused by actual obstruction of the artery. The anoxemia is no longer relative and transient, it is permanent and absolute (disregarding compensatory anastomoses that may later develop). The frequency of occurrence of acute coronary occlusion at night is purely a question of chance. An obstruction is just as likely to form during the night as during the day. The usual absence of nocturnal pain in angina is conditioned solely by the fact that the patient is at rest; he does not undertake any effort sufficient to bring on pain. It is unnecessary to enter into a detailed explanation of the other manifestations of acute coronary occlusion: fever, leukocytosis, pericarditis, etc. These symptoms can all be explained as being the result of the presence of dead tissue in the myocardium, and the effects of the sudden devitalization of a greater or lesser part of the myocardium.

An analysis of the apparent differences between "coronary disease" and angina pectoris reveals that these differences are entirely dependent on the differences in degree of anoxemia of the heart muscle in the two conditions. We repeat that in angina pectoris the anoxemia is relative and transient. It disappears when the cause of the anoxemia, increased work of the heart, disappears. In acute coronary occlusion, the anoxemia is absolute and permanent. The blood supply is shut off, and effort is no longer necessary to bring on anoxemia. Acute coronary obstruction is prolonged angina pectoris. It is, in fact, exactly what it used to be termed before the clinical picture of coronary occlusion was well understood, status anginosus. It is, however, something more than a severe, prolonged attack of angina, for the simple reason that the permanency and degree of the anoxemia introduce another factor, myocardial infarction, and the events that depend on this development.

ANGINA PECTORIS AND OTHER TYPES OF CARDIAC PAIN

We have stated before that the term "angina pectoris" should be applied only to the condition that corresponds to the one described by Heberden, characterized by a more or less typical pain and by the likelihood of termination by sudden death. We have insisted on the essentiality of this second feature, because we believe the evidence is

sufficiently strong to attribute its occurrence to the same underlying cause that brings on the pain, anoxemia of the heart muscle.

There is not any doubt that there are other types of cardiac pain which closely simulate "true" angina pectoris. One may add that in some instances the pain may be indistinguishable clinically from the pain of the condition described by Heberden, at least by our available methods. Yet these pains do not merit the name "angina pectoris" since they do not have the same cause. They do not depend on a disturbance of function that may lead to sudden death. The fact that the pain may closely resemble that of angina pectoris need not lead us astray in our formulation of a conception of the pathogenesis of angina. Is it unreasonable to assume that the stimulus that gives rise to the pain in these cases, irrespective of the cause of the pain, reaches the same nervous paths that are brought into play in Heberden's angina, and hence produces pain of essentially the same distribution? Yet it must not be assumed that pain occurring in a certain region of the chest and radiating in a characteristic way is necessarily synonymous with the condition called angina pectoris.

We may illustrate our meaning by an analogy. The pain of duodenal ulcer has certain well defined features that are well known and need not be enumerated. It is a matter of common experience that identical symptoms may be caused by conditions other than duodenal ulcer. To carry the analogy further, it can be stated that one great difference between these conditions and duodenal ulcer is that in the former there is no possibility of the occurrence of certain events that may distinguish the latter, namely, the occurrence of hemorrhage or perforation. In spite of the similarity in symptomatology, the pathologic basis for the full development of the clinical picture of duodenal ulcer is not found in these other conditions. No one considers them the same in spite of the clinical resemblance.

We do not wish to enter into a discussion of the differential diagnosis of angina pectoris. This has been ably done before. We do wish to emphasize that the condition described by Heberden has a definite and single cause, anoxemia of the heart muscle. The problem of angina pectoris is not to determine what may be its cause.[85] It is to determine, whether, in a given case, angina pectoris is actually present. When the diagnosis is reached, there should be the implication that anoxemia of the heart muscle is present and that sudden death may ensue. This statement is not a mere play on words. It is the attempt to define the nature of the malady clearly described by Heberden. If we substitute "anoxemia" for "coronary disease," the aphorism of Huchard is true:

85. We do not mean that it is unimportant to determine the etiology of the lesion producing anoxemia of the myocardium. If this is found to be syphilis, for example, striking therapeutic results may be obtained by appropriate measures.

"There is only one angina pectoris, the angina pectoris due to anoxemia of the myocardium. All others are false."

CONSIDERATION OF CERTAIN PROBLEMS CONCERNED WITH THE ANOXEMIA THEORY OF ANGINA PECTORIS

A certain number of questions come to mind with regard to the relation of anoxemia to angina pectoris, some of which can be answered, and others of which must be left to future solution. Why, for example, should anoxemia ever occur in the heart muscle in a case of coronary disease, if there are anastomoses between the coronary arteries, and if the Thebesian vessels can nourish the heart muscle even when the coronary arteries are completely obstructed? It is true that the myocardium may not suffer any apparent injury in the presence of a marked occlusion of one or even both coronary arteries. But the fact remains that myocardial injury does occur in many instances, and the problem is to determine not whether anoxemia of the myocardium may occur, but rather under what circumstances it does occur. The question has been well answered and summarized by Oberhelman and LeCount to whose work we have already referred: infarction following coronary obstruction depends on the rapidity of the vascular occlusion and the richness of the preexistent anastomoses. In addition, Wearn's work has showed that a third important factor is the extent to which the Thebesian vessels may take up the burden of nourishing the myocardium. We have the two extremes: in the one case, complete compensation for an obstruction of the coronary artery, so that the patient does not suffer any symptom and the heart muscle does not undergo any change as a result of the vascular occlusion; in the other case, myocardial infarction takes place. Between these two extremes lie the various gradations of symptoms and pathologic damage that may be present in angina.

A much more difficult problem is to determine why angina pectoris develops in such a relatively small percentage of the patients with aortic insufficiency, all of whom have a lowering of the diastolic pressure, and hence, presumably, a reduction of the coronary flow. Does the reduction of the coronary flow necessarily mean a reduction of blood supply to the myocardium? The rôle of the Thebesian vessels under these circumstances is not known, and it is possible that the extent to which these vessels may compensate for the reduced coronary flow may play some part in determining whether angina develops. One fact of clinical interest tends to demonstrate that aortic insufficiency does act by diminishing the coronary blood supply. Angina pectoris is much more common in syphilitic aortitis when both aortic insufficiency and occlusion of a coronary ostium are present, than when the latter lesion alone exists. In other words, the valvular lesion adds something to favor the development of angina, and it is logical to assume that this factor is the

diminution in blood supply through the coronary arteries. In addition to the question of the rôle of the Thebesian vessels, a second factor of considerable importance in this connection is the probable variation in the capacity of the heart muscle to resist the effect of anoxemia (to incur an "oxygen debt"). These two factors, the degree of compensation through the Thebesian vessels, and the individual variation in the myocardial tissue to withstand anoxemia, in addition, of course, to the extent of the valvular lesion, are probably important in determining whether or not angina appears in a case of aortic insufficiency. However, at the present, there is no definite answer to this problem, and the same holds true for the question of angina in pernicious anemia. What we have attempted to do is to show that in every case of genuine angina pectoris there is a lesion that may produce anoxemia of the myocardium, and that anoxemia of the myocardium may account for all the characteristic manifestations of angina; conversely, angina does not develop in the absence of anoxemia, and theories which assume some other derangement of function do not explain the characteristic features of angina. We do not yet know under just what circumstances anoxemia will affect the myocardium so that angina will appear, or by what mechanism anoxemia calls forth a paroxysm of pain. But these uncertainties do not differ materially from innumerable similar ones in clinical medicine, even in conditions that are well understood. It is generally agreed that "mountain sickness" is caused by anoxemia; yet symptoms appear in one person, and fail to appear in another, when both are subjected to the same degree of anoxemia (lowered oxygen tension). To say that the extent of the symptoms depends on the completeness of compensation for the anoxemia is no more than saying the same about the appearance of angina pectoris when there is anoxemia of the myocardium.

One is often confronted by a clinical case, the features of which are suggestive of angina pectoris in certain respects, and atypical in others. Are they cases of genuine angina? The question is, of course, of the utmost importance, but it is, nevertheless, no real concern of the issue at hand. It is one that has to do with diagnosis, and not with the pathogenesis of angina. Unfortunately there is not, at present, an absolute criterion of diagnosis of angina pectoris. So far as we know, the decision in an individual case must be determined by the outcome. If a patient with atypical symptoms of angina dies instantaneously, the presumption is that the patient actually suffered from angina during life, and that a lesion producing anoxemia will be found at necropsy. If the patient does not die instantaneously, or if he does not develop the typical clinical picture of acute coronary occlusion, there must be a certain amount of doubt about the diagnosis.

We have stated that the paroxysms of pain in angina pectoris are provoked by increasing the demands on the heart and relieved by dimin-

ishing the work of the heart, and that a case of angina is likely to terminate by sudden death. This rule applies to most cases, and it remains to discuss the exceptions. These exceptions are more apparent than real.

Cases Characterized by Spontaneous Development of Pain.—Although angina is usually initiated by some factor whose influences on the demands of the heart are obvious, such as effort or emotion, there are other instances in which the angina seems to arise spontaneously, as during rest or sleep. Certain of these cases can be dismissed at once, namely, those due to acute coronary obstruction. We have already pointed out the relation of these cases to angina, and further elaboration is unnecessary. Angina is really caused by a disproportion between the demands on the heart and the oxygen supply to the heart. In these cases, the oxygen supply is suddenly reduced below the requirements of the heart of even the resting person.

There are other cases not due to acute coronary obstruction. The exact physiologic changes that precede the attacks of pain are not known. However, the observations of MacWilliam [86] are of importance in this connection. They have demonstrated that sudden elevations of blood pressure or sudden increases in heart rate may occur during sleep, particularly disturbed sleep. These sudden changes may be as marked as those that occur during moderate exercise. Moreover, the reduction of blood pressure during such attacks is frequently followed by a rapid disappearance of pain (Mackenzie,[12] case 17; Schwartz [87]). In other words, the changes in the circulation causing increased work of the heart may arise without effort, and they explain, in part at least, why angina occasionally arises during rest.

There is another group of cases that seems to be closely associated with attacks of paroxysmal dyspnea. That is to say, certain patients who suffer from paroxysmal dyspnea frequently have nocturnal attacks of angina. Indeed, angina may occur only at night in these patients. Without going into a discussion of the still disputed subject of paroxysmal dyspnea, it may be said that it has been shown that the attacks are preceded by a gradual increase in heart rate, blood pressure and circulatory minute volume (Eppinger, von Papp and Schwarz [88]). It is conceivable that many of the attacks of nocturnal angina, occurring

86. MacWilliam, J. A.: Some Applications of Physiology to Medicine: III. Blood Pressure and Heart Action in Sleep and Dreams, Their Relations to Hemorrhage, Angina and Sudden Death, Brit. M. J. **2**:1196 (Dec. 22) 1923.

87. Schwartz, S. P.: Paroxysmal Cardiac Pain, Am. Heart J. **2**:497 (June) 1927.

88. Eppinger, H.; von Papp, L., and Schwarz, H.: Ueber das Asthma Cardiale, Versuch zu einer peripheren Kreislaufpathologie, ed. 1, Berlin, Julius Springer, 1924.

in people subject to paroxysmal dyspnea, are brought on by these circulatory changes that precede and accompany paroxysmal dyspnea. Angina occurs, however, only in those who are already predisposed by other lesions that reduce the oxygen supply to the heart, such as coronary disease or aortic insufficiency.

Cases Characterized by Attacks not Rapidly Relieved by Rest.—Little need be said about the long duration of the anginal attacks in coronary occlusion: the anoxemia is permanent and constant, and hence unaffected by rest. It is also a matter of experience that nocturnal attacks, even when they are not caused by coronary occlusion, are often of rather long duration. We think it likely that most of the cases occur in persons subject to paroxysmal dyspnea, and that the long duration of the anginal attacks may be due to the continued increase in circulatory minute volume that occurs before and during the attacks of paroxysmal dyspnea, whatever may be the fundamental cause of the increased circulatory minute volume. This relationship between certain attacks of angina and paroxysmal dyspnea has been recently pointed out by Braun.[89]

Cases not Ending by Sudden Death.—In some cases, the outcome is not by sudden death. Exclusive of those patients who die of some intercurrent infection or other unrelated malady, practically all others die because of failure of the heart muscle. Some develop coronary occlusion and the condition is terminated by rapidly progressive myocardial insufficiency. In others, the myocardial damage is less abrupt, and death ultimately occurs with the common picture of chronic progressive failure of the heart muscle. These latter cases furnish the examples for the statement that angina tends to disappear when heart failure supervenes. The explanation, as Mackenzie has stated, is undoubtedly due to the fact that when myocardial failure develops in these patients, their activities are so restricted on account of dyspnea and other disabilities that they are unable to exert themselves sufficiently to bring on pain.

Reference to charts 1, 2, 3 and 4 may illustrate our meaning more clearly. The figures are simple diagrammatic representations of what takes place in a patient suffering from dyspnea or angina, or both. Chart 1 shows the gradual steady increase in dyspnea, proportionate with the increase in effort.[90] After a certain amount of effort the stage

89. Braun, F.: Ueber die Kombination von Asthma cardiale mit Angina Pectoris, Wien. klin. Wchnschr. **40**:1278 (Oct. 13) 1927.

90. By effort, is really meant a certain effort in a given unit of time. That is to say, a certain task in a certain time may bring on dyspnea; a similar task in twice the time may cause no dyspnea. The same principle holds true for the causation of pain. By incapacity is meant inability on the part of the patient to continue his effort. The diagrams are not intended, of course, to be absolutely accurate. They are sufficiently accurate, however, to illustrate the points at issue.

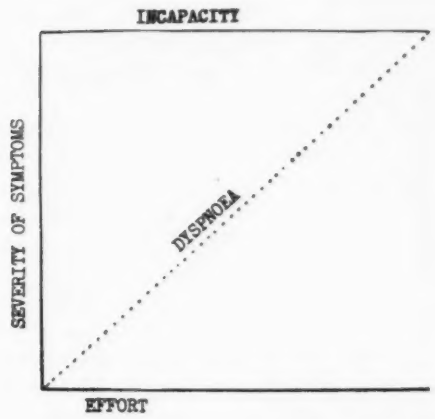


Fig. 1.—Illustrating the gradual increase in dyspnea, which is proportionate to the effort expended.

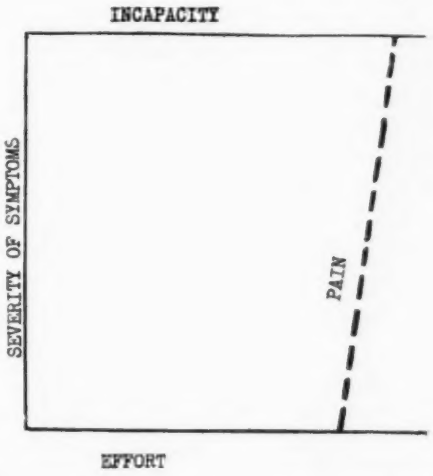


Fig. 2.—Illustrating the freedom from pain up to a certain point and then the sudden appearance of the symptom which increases to incapacitating intensity in a short time.

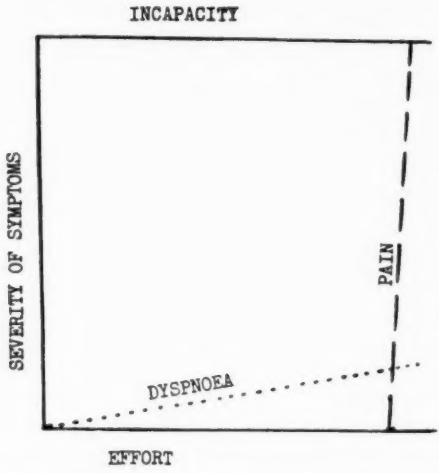


Fig. 3.—Illustrating the course of events in a patient suffering chiefly from angina pectoris, but also from a mild degree of myocardial insufficiency. The dyspnea increases gradually, but before this symptom has become severe enough to limit the effort of the patient, pain suddenly appears and reaches an incapacitating intensity.

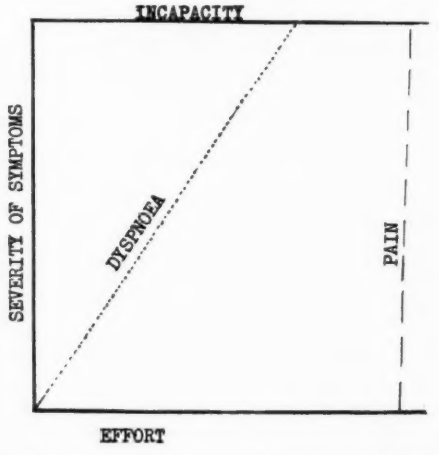


Fig. 4.—Illustrating the course of events in a person suffering from angina pectoris and severe myocardial insufficiency. In this case, breathlessness increases so rapidly that the stage of incapacity is reached before pain has had a chance to develop. The patient loses his symptoms of angina until myocardial function is sufficiently recovered and the effort to produce incapacitating pain again becomes less than the effort to produce incapacitating dyspnea. Pain is represented by a light dash instead of a heavy dash to indicate that it actually does not occur under the foregoing circumstances. Pain is indicated merely to draw its relation to dyspnea.

of incapacity is gradually reached, and the patient comes to a halt. Chart 2 shows the development of pain in a patient suffering from angina. It is meant to demonstrate that up to a certain point, effort does not cause any symptom of warning. Suddenly pain appears, and typically this pain reaches an incapacitating intensity with striking rapidity. Chart 3 demonstrates the development of pain and dyspnea in the same patient, the pain being the outstanding symptom. It shows that dyspnea does not become a prominent symptom in such a person, since incapacitative pain appears before dyspnea of any marked severity has had a chance to develop. Chart 4 illustrates the disappearance of pain in a person suffering from marked dyspnea (myocardial insufficiency). The dyspnea increases as it usually does, gradually and proportionately with the effort. But in this case, it increases so rapidly that incapacitation through dyspnea takes place before pain has had a chance to develop.

Finally, there are cases characterized by long remissions, in some of which cures are practically obtained. Gallavardin [10] recorded thirty-eight cases in which there were remissions ranging from a year and a half to eighteen years. It seems probable that the freedom from pain is due to the development of anastomotic channels, with temporary and possibly permanent relief of the anoxemia of the affected heart muscle.

It may be seen, therefore, that the exceptions to the rule that angina is provoked by effort, rapidly relieved by rest, and likely to end in sudden death, are more apparent than real. Certainly in most cases, an adequate explanation for the exception can be found.

SUMMARY AND CONCLUSION

A critical analysis of the theories that attribute angina pectoris to coronary spasm, to disease of the aorta or to myocardial exhaustion demonstrates that these views are open to such serious criticism that they become unacceptable; on the other hand, it can be shown that anoxemia of the heart, in the sense in which we have employed the term, explains every characteristic of angina, including the likelihood of sudden death, which must be considered an integral feature of the condition. The percentage of instances in which conditions capable of producing anoxemia of the myocardium have been found in cases of undoubted angina is so high that the accuracy of the diagnosis in the few remaining instances seems open to question. We feel that an eclectic theory which admits a varied basis for angina should be abandoned. The angina pectoris of Heberden has but one cause, anoxemia of the myocardium.

Billings Hospital, University of Chicago, 58 South Street.

FEVER IN GASTRIC AND IN DUODENAL ULCER*

SOPHUS BANG, M.D.
Professor, Physician-in-Chief, Municipal Hospital
COPENHAGEN, DENMARK

It often happens that the clinical symptoms of a disease are not in accordance with the organic lesion actually present. This fact is conspicuous in stomach diseases. To see achylia develop without any subjective symptoms is an everyday experience. The symptoms of gastritis do not develop simultaneously with the pathologic-anatomic changes in the mucous membrane of the stomach. Even such a lesion as cancer of the stomach is frequently free from any definite symptoms for a long time. This variation of symptoms is particularly characteristic of the gastric and duodenal ulcers. In some cases one finds violent pains and fatal hemorrhages, in others there is a complete absence of symptoms, mostly periodic, but sometimes throughout the course of the disease. This behavior can be so constant that periodic latency is diagnostic in certain forms of ulcer. In such a case, however, the pathologic-anatomic picture is in keeping with the symptoms, as it is mostly characterized by negative observations. The classic description of ulcer of the stomach suggests the picture of a simple defect of the mucous membrane with no reaction about it, and this fact is indicated by the term "ulcus simplex."

In the last six or seven years, however, this classic "simplicity" in the anatomic relations of ulcer of the stomach has encountered increasing criticism, which I shall discuss later. As to the clinical symptomatology, on the other hand, there has not been great progress in the last generation, in spite of the marked development of methods of examination. Methods are lacking for the determination of when the ulceration takes place, when it is healed and what really does happen in the latent periods. I have attempted to attack this problem from various angles, but here I shall discuss only an analysis of the temperature in gastric and duodenal ulcers.

The fact that fever occasionally is present in ulcer is not altogether unknown. But it has not received the attention it deserves with regard to its diagnostic and practical significance. I have not found this subject mentioned in any of the many textbooks I have examined. From this fact I conclude that the occurrence of fever in gastric ulcer is not generally known. The special literature on ulcer of the stomach mentions now and then that fever can be associated with hemorrhages, but so far

---

*Lecture delivered at the Northern Medical Congress in Copenhagen, July, 1927.

I have succeeded in finding only one paper which mentions fever as a complication of nonbleeding ulcers. This was an article by Kroner,[1] which appeared recently. He cited one earlier author, Lorenz, who was said to have found fever in 23.5 per cent of his 179 patients with ulcer of the stomach. Kroner studied 300 patients with ulcers from Strauss' department in Berlin, and found fever, without any demonstrable cause, in 17.5 per cent of them. It should be mentioned, however, that Kroner regarded a single rise of temperature to 37.5 or 37.6 C. as fever.

My material comprises 386 cases from the Municipal Hospital (Copenhagen), department III, during the years 1922-1926. This number includes all the cases I diagnosed as ulcer. I investigated the frequency of fever in these cases, and I did not consider an isolated rise of temperature as "fever," no matter how high the temperature rose. I have included only those patients in whom the fever lasted several days. I found these fever periods in 207 of the 386 patients, that is, in 51.5 per cent. Naturally one must exclude all cases in which there was the slightest indication that the fever might have been due to causes other than the lesion in the stomach. For that reason, I analyzed each individual case report, and found that twenty-eight cases had to be left out (among these were active and suspected cases of pulmonary tuberculosis, pyelitis and cholelithiasis. In addition there were seven patients in whom the temperature rose shortly before the onset of menses, so that a premenstrual rise of temperature had to be taken into consideration).

After these cases are deducted, my material includes 358 patients, of whom 179 had fever, that is, 50 per cent. The fact that I found fever in 50 per cent of the patients while Kroner found fever in 17 per cent might well be due to differences in the kinds of lesions. It is reasonable to assume that the fever is less frequent in old and latent lesions than in acute conditions. That there really is such a difference between the two groups is evident on a comparison of the frequency of manifest hemorrhage (hematemesis and melena, but not the occult bleeding). In Kroner's group the hemorrhages occurred in 25 of 300 patients, or 8 per cent; I found hemorrhages in 161 of 386 patients, or 41.7 per cent. As the fever most often is associated with hemorrhage, one will readily understand the difference between the groups. This difference is due to the fact that the Municipal Hospital admits only patients with acute cases. This might also explain why the specialists in diseases of the stomach have not attached so much importance to the fever, as the patients who consult them usually are those in whom the condition is chronic.

1. Kroner: Ueber Fieber bei Ulcus ventriculi et duodeni, Deutsche med. Wchnschr. **52**:1777, 1926.

Leube mentioned the complication of fever in gastric ulcer, but he considered the fever an exception. Eichhorst (1887) clamed occasionally to have seen a mild fever when the intestines contained a large amount of blood after hematemesis but as the temperature returned to normal on elimination of the blood, he regarded the rise of temperature as an absorption fever. Strümpel stated that a slight rise of temperature, the so-called anemic fever, was common subsequent to hematemesis. However, Otto Leichtenstern [2] (1891) was the first one to investigate this relation systematically, and he used the term "febris methematemetica," which he defined as "a fever that sometimes is quite mild, sometimes rather high, sometimes perfectly atypical, irregular and

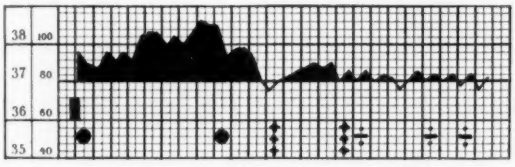


Chart 1.—Gastric ulcer in a man, aged 60. In this and the following curves, all the rises of temperature above 37 C. are filled in black. A black square indicates hematemesis. A black sphere indicates melena. + indicates weak, ++ medium and +++ strong benzidin reaction; ÷ indicates negative benzidin reaction.

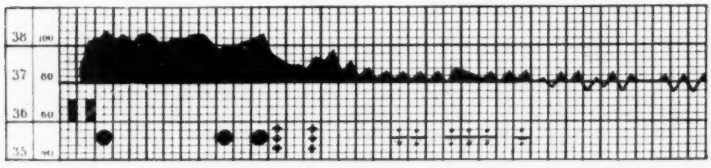


Chart 2.—Gastric ulcer in a man, aged 51.

remittent, sometimes continuous for several days." He found this fever to be a frequent, even a regular, phenomenon in hemorrhages from gastric ulcer, and he regarded it as an absorption fever because it usually did not appear until two or three days after the hematemesis while the patient still was constipated. Most other clinicians who have dealt with this question at all (for instance, Riedel, Stahelin, Ewald,[3] Fleiner) subscribe fully to Leichtenstern's view. I have not found any

2. Leichtenstern: Intravenöse Kochsalzinfusion bei Verblutungen, Samml. klin. Vortr. **25**:260, 1891.

3. Ewald: Magenkrh., Eulenburg's Realencyklopädie der gesammten Heilkunde, Vienna and Leipzig, Urban & Schwarzenberg, 1897, vol. 14, p. 287.

tables that illustrate this question except in a report by Jacobs [4] and in the recent work by Kroner, who found fever in eleven of twenty-five patients with manifest hemorrhages, i.e., in 45 per cent. This figure is considerably lower than that of my group, probably owing to the more acute character of my cases.

In my 358 cases I have taken into account only those hemorrhages which were definitely demonstrated in the hospital. Hemorrhages which occurred while the patients were at home without subsequent occult bleeding in the hospital are not included. There are 138 cases of definite hemorrhage, and fever was associated with the hemorrhage in 125 cases, or 90.5 per cent. In some of these cases, however, a possible source of error must be taken into consideration. Thirty-five of the patients were

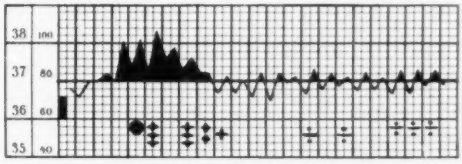


Chart 3.—Gastric ulcer in a man, aged 41.

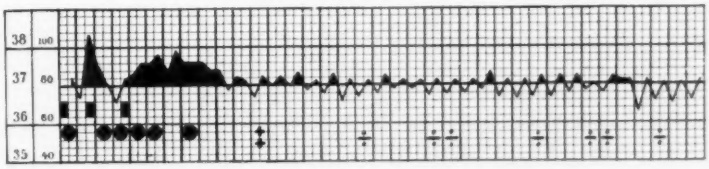


Chart 4.—Gastric ulcer in a man, aged 32.

treated with an injection of gelatin; this procedure can cause a rise of temperature for from one to two days. Thirty-two of the patients, however, had fever previous to the injection of gelatin. Hence, there were only three cases in which the effect of the gelatin cannot be disregarded with absolute certainty. If these three cases are excluded, of a total of 138 patients there remain 121, or 87.5 per cent, in whom fever was present.

CAUSES OF FEVER

What can be the cause of this fever? It can be taken for granted that the anemia in itself did not cause the fever. That this is true is evident from my material, as many patients with a mild anemia had high fever, and numerous patients with a most severe anemia showed a

4. Jacobs, cited by Kroner (footnote 1).

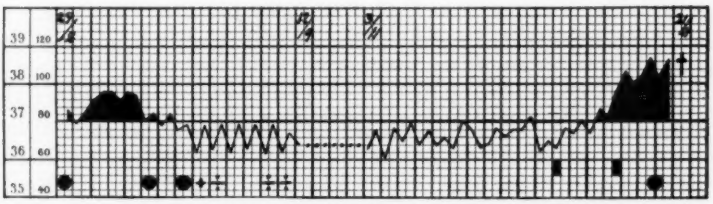


Chart 5.—Man, aged 42. The first rise of temperature occurred in connection with melena. Nearly three months later, hematemesis occurred two times, followed by rise of temperature and death with symptoms of anemia. Autopsy: peptic ulcer of jejunum with erosion of vessel. No other demonstrable cause of elevation of temperature, in vivo or at autopsy.

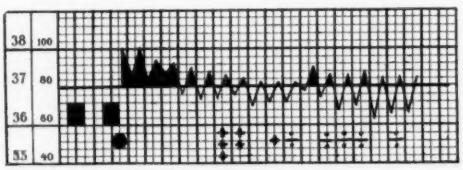


Chart 6.—Juxtapyloric ulcer in a man, aged 45.

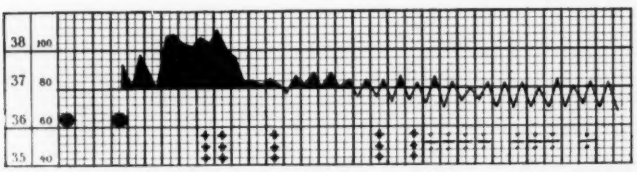


Chart 7.—Juxtapyloric ulcer in a man, aged 53.

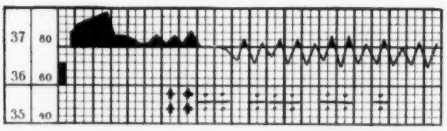


Chart 8.—Gastric ulcer in a man, aged 48.

marked rise of temperature only for a few days after the hemorrhage, while the anemia persisted or even increased without any fever. A comparison of the patients with and without fever might give some information on this subject. The blood was examined immediately after the hemorrhage in nine patients who did not have subsequent fever. The hemoglobin percentage was 55 or more in all of them. In the febrile cases, the hemoglobin content was above 55 per cent in seventy-two patients and below 55 per cent in thirty-four patients. Kroner's result is analogous to mine. But when Kroner concludes from this result that the fever is dependent on the "violence" of the hemorrhage, I cannot agree with him. For, if the hemorrhage and the fever

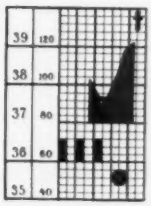


Chart 9.—Hematemesis and death with symptoms of anemia in a woman, aged 44. Autopsy showed: ulcer of small curvature with erosion of artery. Other observations at autopsy were negative.

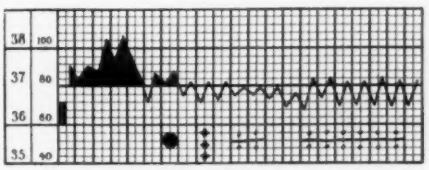


Chart 10.—Juxtapyloric ulcer in a man, aged 39.

are caused by the same process (inflammatory, for instance), then this process might conceivably have accomplished the "violence" of the hemorrhage and the fever alike, without these being directly dependent on each other. Two of my afebrile cases are of interest in this connection, both patients having had profuse hemorrhages which caused death in a few days. In neither did the temperature exceed 37.2 C. Autopsy revealed in both instances that an erosion of the vessel wall was the cause of the profuse hemorrhage. One can readily understand that when these ulcers did not cause a rise of temperature previous to the hemorrhage, fever would not necessarily result from the minimal erosive process that is required for the perforation of a vessel already laid bare. On the other hand, in an acute and febrile inflammatory process, which

rapidly destroys the mucous membrane and in doing so perforates a vessel, "violent" hemorrhage and fever can appear simultaneously without being caused by each other. In the last ten years in the department, autopsy material was obtained from five patients who had died from hemorrhage in ulcer of the stomach without the temperature rising shortly before death. In all these cases the ulcers were old and callous.

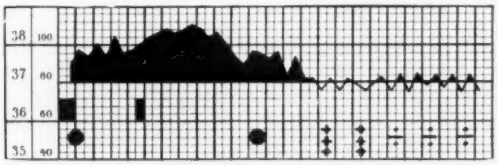


Chart 11.—Duodenal ulcer in a man, aged 63.

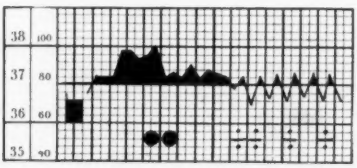


Chart 12.—Gastric ulcer in a woman, aged 64.

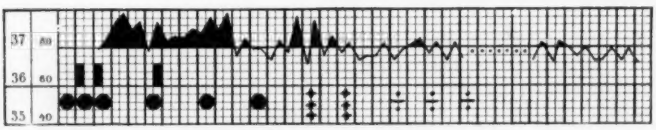


Chart 13.—Gastric ulcer in a man, aged 32.

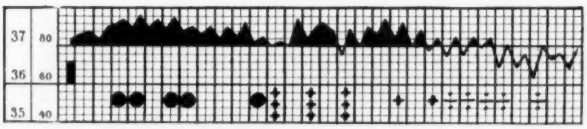
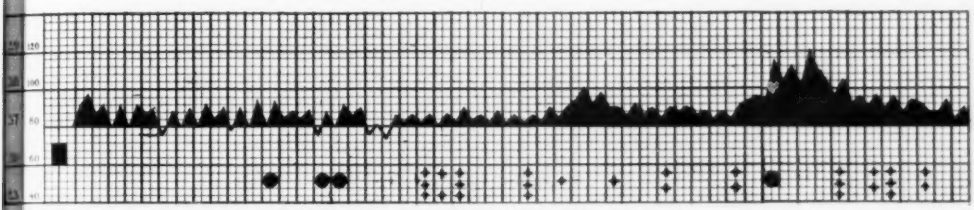


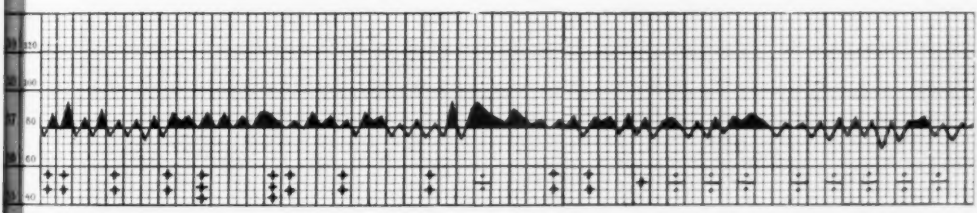
Chart 14.—Gastric ulcer in a woman, aged 52.

In three death occurred from the erosion of a dissected artery at the bottom of the ulcer. In addition, I have one case in which an operation revealed a callous ulcer with some scar formation. Large hemorrhages had occurred repeatedly, without any fever, about three weeks previous to the operation. If this point of view is correct, one would expect the afebrile hemorrhage to be most frequent in old ulcers; and I found that

twelve of the thirteen patients with afebrile hemorrhages had ulcer symptoms for several years (from two to thirteen years). In only one case were the symptoms of a recent date (two months). On the other hand, all the apparently recent ulcers were found in the febrile group, namely, nineteen patients, in whom the first symptoms had appeared within the week before examination (the hematemesis was practically the first symptom in the stomach in these cases). Collecting all the febrile cases with first symptoms of not more than two months' duration on admission, I find ninety-two patients in this group, that is, 74 per cent. Thus all the recent ulcers occur in patients of the febrile group, while old ulcers are found both in the febrile and the afebrile groups. Fever is fre-



A



B

Chart 15.—Gastric ulcer in a woman, aged 55. The hemorrhage lasted eighty-nine days, the rise of temperature, ninety-six days.

quently associated with an acute exacerbation of the old process. But, of course, old ulcers can also give rise to fever when they become secondarily infected. My experience demonstrates, I believe, that acute ulcers and acute exacerbations of old ulcers frequently are connected with fever, apart from the fever of secondary infection.

I have tried to answer the question whether absorption or decomposition of large amounts of blood in the intestines can give rise to fever. For that reason I have compared the ulcer with other conditions in which a great deal of blood is poured into the intestines. The hemorrhages from esophageal varices seem most appropriate for such a comparison. During the last ten years I have performed seventeen autopsies

in which esophageal hemorrhage was the cause of death. Three of the patients had complications which gave sufficient cause for the fever present, and in one patient the temperature was taken once only (37.9 C.) shortly before death. The temperature was normal in the remaining thirteen patients for from one to four days after the start of the hemorrhage. Most of these patients, however, died in from one to three days after admission, and the others soon developed febrile complications (bronchopneumonia, otitis, phlegmons). In only two patients did the temperature remain normal for four days after the onset of the hemorrhage. This did not happen once after a severe hemorrhage in my patients with ulcer of the stomach. Autopsy was not performed on seven patients who died of hemorrhage from esophageal

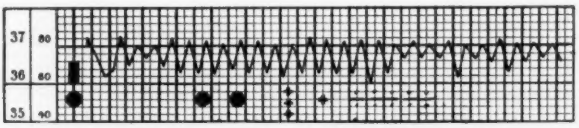


Chart 16.—Hemorrhage from esophageal varices in a man, aged 48.

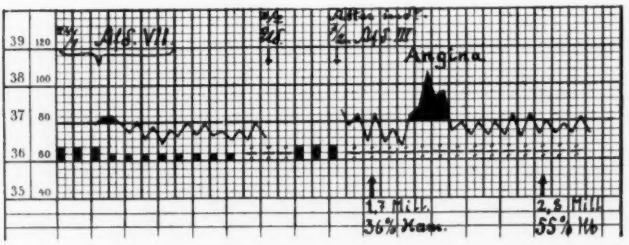


Chart 17.—Epistaxis in a man, aged 48. In this chart the black squares indicate bleedings from the nose. At the cessation of bleedings he had 1,700,000 red corpuscles. That the anemia was due to the bleeding is evident, as he had 2,800,000 red corpuscles ten days later.

varices. Four of these had complications which explained the mild fever; the other three had a normal temperature throughout. In one of these patients (fig. 16) the number of red blood cells decreased to 2,500,000. In the patients with ulcer such a case did not occur without fever. Of course, the diagnosis of hemorrhage from esophageal varices is never absolutely sure without an autopsy, but such a case proves that large amounts of blood can pass through the intestines without causing fever.

The hemorrhages from cancer of the stomach generally are not suitable for comparison, because the amount of blood usually is small, and because fever often develops without hemorrhage. However, I

encountered twelve patients with cancer of the stomach with severe hematemesis. Five of these had a normal temperature for at least six days after the hemorrhage. One would think that epistaxis would be suitable for comparison, but most of my cases cannot be used for this purpose because the case reports do not indicate how much blood passed through the intestines. Only two of my cases allow any conclusion in that respect: In the first case, for two weeks the hemorrhage was sometimes profuse, sometimes continuously oozing; the count of red corpuscles decreased to 1,700,000. Nevertheless, the temperature remained normal (apart from a complicating angina [fig. 17]). In the second case, the temperature remained normal for five days after an epistaxis, which was followed by several tar-colored stools.

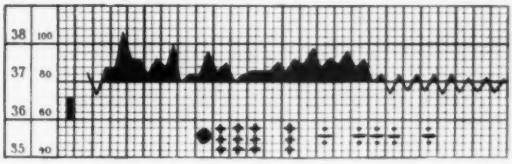


Chart 18.—Gastric ulcer in a woman, aged 74.

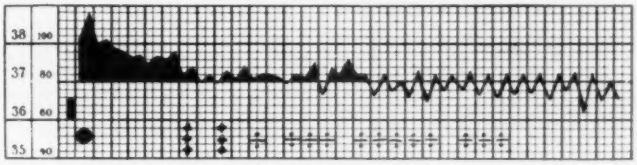


Chart 19.—Gastric ulcer in a man, aged 38.

Finally, I saw seventeen patients with hemorrhage from gastric ulcer without rise of temperature. This proves that not every accumulation of blood in the intestines causes fever.

The entire control material needs to be increased and additional investigations must be carried out before one can definitely decide the question whether accumulation of blood in the intestinal tract can of itself give rise to fever; but even from the material at hand, one can conclude that not every accumulation of blood in the intestinal tract is followed by fever. And, fortunately, my experience with ulcers gives some information on this question.

If the blood in the intestines were the only cause of the fever, one would expect a certain relation between the rise of temperature and the retention of the blood in the intestinal tract. And such a relation must be present in one respect, namely, with regard to the height of the fever. The highest temperature was usually present while the patient was kept

constipated, as Eichhorst has already observed. In my patients the fever frequently subsided at the same time that the first bowel movement occurred, but this was not conclusive, as I tried to keep the patients constipated until they felt perfectly well, i.e., until the fever ceased. I found it likely that decomposition of the blood in the intestines caused fever or at least increased a preexisting fever, but the fever was not at all proportionate to the amount of blood in the intestines. The elevated tem-

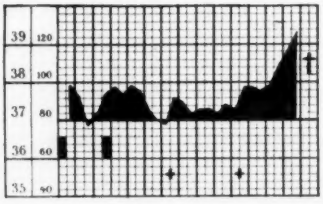


Chart 20.—Woman, aged 68. Autopsy: Ulcer of small curvature. No other demonstrable cause of fever.

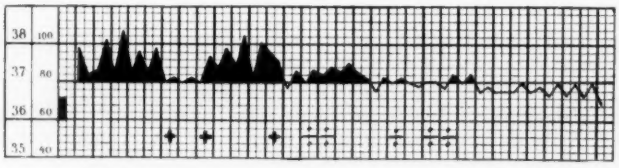


Chart 21.—Gastric ulcer in a woman, aged 20.

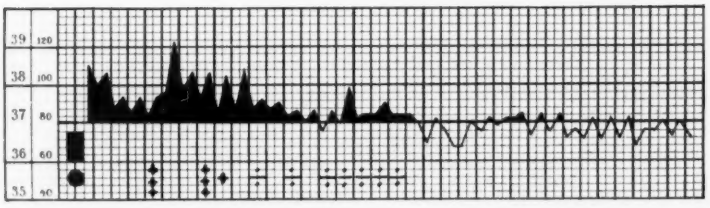


Chart 22.—Juxtapyloric ulcer in a man, aged 39.

perature persisted in a number of cases a long time after the last trace of blood had disappeared from feces, and the test was done with the sensitive benzidine reaction (figs. 18 to 32). This relation was found in 68 of 138 cases, and was indicated in many more cases.

However, one can proceed a step farther. One can examine those cases in which neither hematemesis nor melena were present, and in which the occult bleeding could be demonstrated only with benzidine

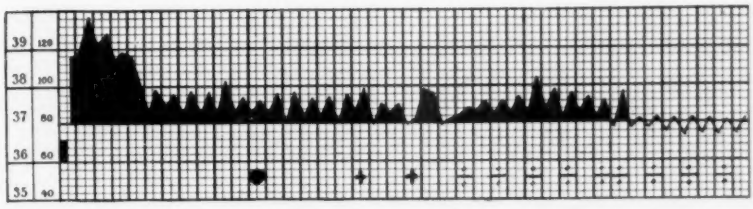


Chart 23.—Gastric ulcer in a woman, aged 39.

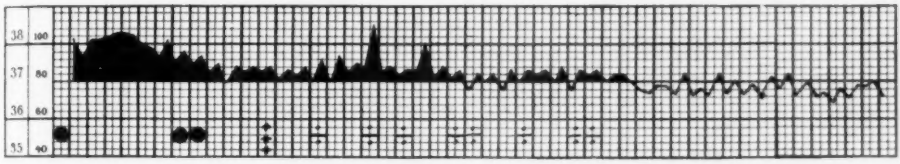


Chart 24.—Juxtapyloric ulcer in a woman, aged 33.

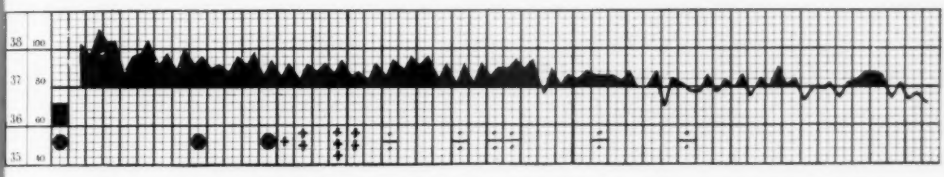


Chart 25.—Gastric ulcer in a woman, aged 47.

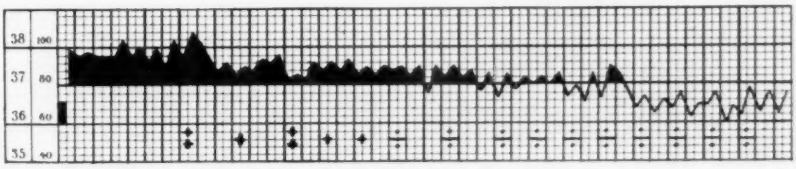


Chart 26.—Juxtapyloric ulcer in a woman, aged 67.

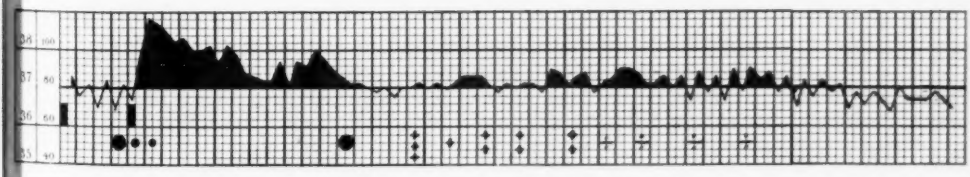


Chart 27.—Duodenal ulcer in a man, aged 67.

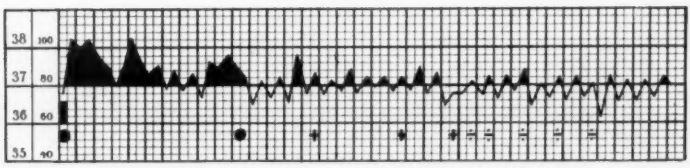


Chart 28.—Duodenal ulcer in a man, aged 30.

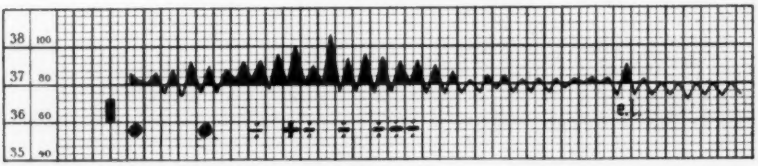


Chart 29.—Gastric ulcer in a man, aged 41.

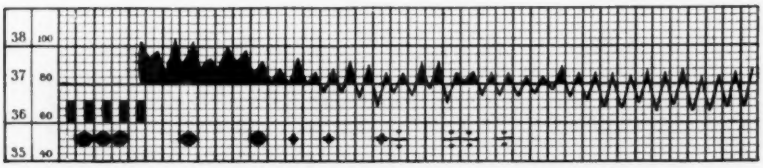
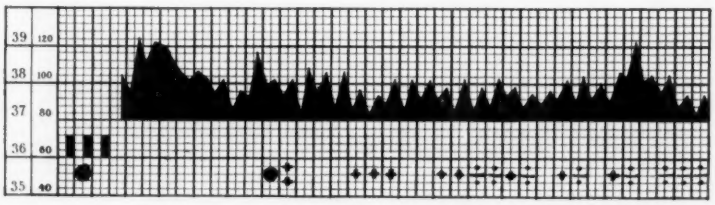
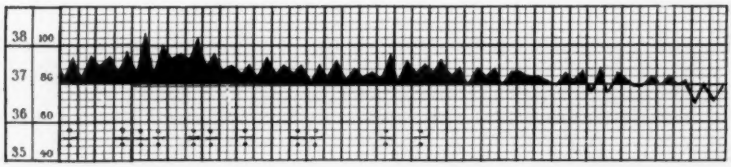


Chart 30.—Juxtapyloric ulcer in a man, aged 55.



A



B

Chart 31.—Juxtapyloric ulcer in a woman, aged 64.

(figs. 33 to 37). According to Gregersen, the weakest benzidine reaction indicates a total of 1 Gm. of blood in the entire intestinal tract; and it is not possible that such small amounts of blood can cause fever from absorption or decomposition. I have seen twenty-eight such cases of occult bleeding, and twenty-one of these, or 75 per cent, were febrile. The bleeding could not be considered established in three of the twenty-eight patients, as the benzidine reaction was positive only once, i.e., immediately after admission; thus the reaction can have been due to the

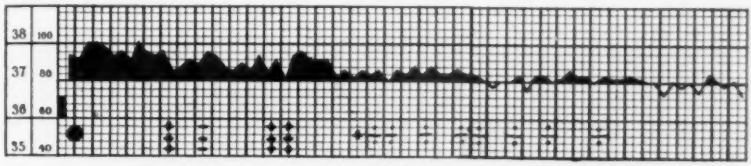


Chart 32.—Juxtaplyoric ulcer in a man, aged 45.

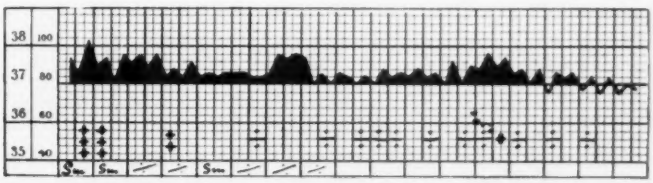


Chart 33.—Ulcer of small curvature in a woman, aged 75.

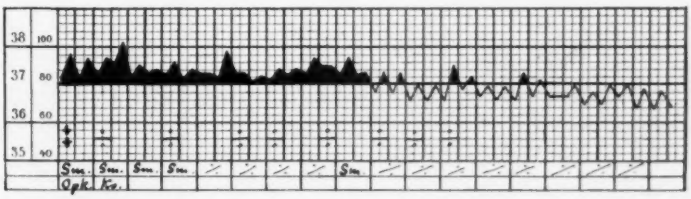


Chart 34.—Juxtapyloric ulcer in a man, aged 51.

consumption of meat before admission. If these three patients are left out, the fever percentage rises to 84 per cent; and this is about the same fever percentage as that in manifest hemorrhages.

In order to prove that the fever is due to some cause other than the hemorrhage, one should demonstrate the presence of fever in patients with ulcer but no hemorrhage (figs. 38 to 44). In the 386 patients with ulcer, there were 13 of this type. When one considers that 40 per cent of the 386 patients were admitted to the hospital because they had

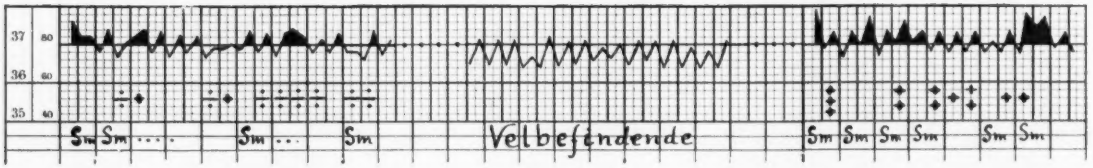


Chart 35.—Ulcer of small curvature in a man, aged 49. Sm. means pain; Velbefindende, no symptoms. That the temperature elevation was not due to the pains is evident, as the pains did not set in before night, while the temperature rose in the evening.

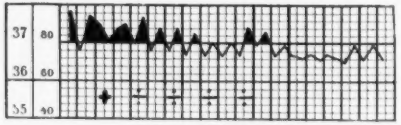


Chart 36.—Juxtapyloric ulcer in a man, aged 45.

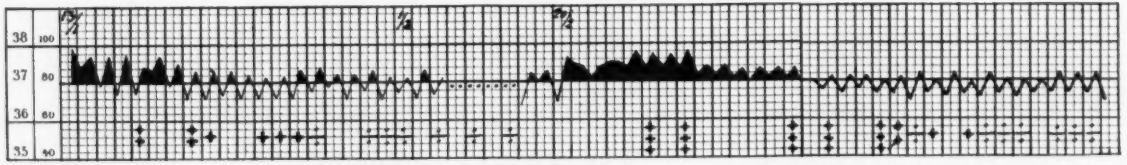


Chart 37.—Duodenal ulcer in a man, aged 37.

manifest hemorrhage, thirteen is not such a small number. They comprise 6.5 per cent of the patients with nonbleeding ulcers. It is a foregone conclusion that the large majority of chronic latent ulcers are afebrile. Autopsy was done on two of the thirteen patients with febrile nonbleeding ulcers. Both ulcers were old, large and callous, with a foul base. In such cases it is reasonable to assume that the ulcer was the site of a secondary infection. The other eleven ulcers were juxtapyloric or duodenal. In the group "ulcer with manifest hemorrhage," the diagnosis of juxtapyloric and duodenal ulcer was equally frequent in the febrile and the afebrile groups (50 and 47 per cent, respectively).

From this investigation I think I am justified in the conclusion that many patients with gastric and duodenal ulcer develop a rise of

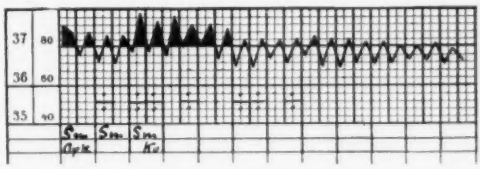


Chart 38.—Duodenal ulcer in a youth, aged 19.

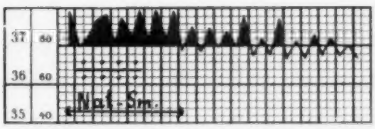


Chart 39.—Duodenal ulcer in a man, aged 29. The rise of temperature was not due to pains, as they occurred at night several hours after the rise of temperature.

temperature which is not associated with hemorrhages. Large amounts of blood in the intestines, apparently, are capable of increasing this fever; and, perhaps, the decomposition of the blood can give rise to fever, but this question requires further investigation. This fever may vary to some extent, but it most decidedly tends to be continuous and with relatively small variations.

I think it will prove of some practical value to take these temperatures into account. In some of my patients, a slight elevation of the temperature was the only demonstrable sign of an otherwise latent period. Even though all other symptoms were absent, the temperature still indicated that the ulcer itself or its fundamental cause had not yet been cured. Since I have realized this fact, I have ordered the patients diet and rest in bed accordingly. A slight elevation of the temperature can sometimes persist for weeks, and I believe it to be of some conse-

quence. There is no reason why one should pay less attention to this temperature than one does in the treatment of tuberculosis. It is doubtful, I believe, that this temperature will prove of value in differential diagnosis, but it is not altogether unimportant that one learn that an ulcer of the stomach can be associated with a fever, which is not unlike the tuberculous fever. At any rate, the presence of fever can no longer be used to differentiate between a hemorrhage from pulmonary tuberculosis and one from an ulcer of the stomach.

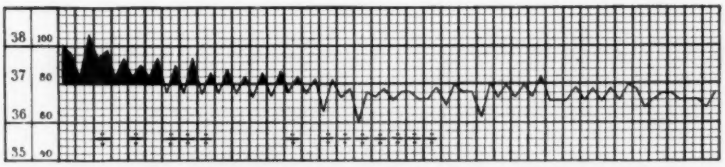


Chart 40.—Juxtapyloric ulcer in a man, aged 53.

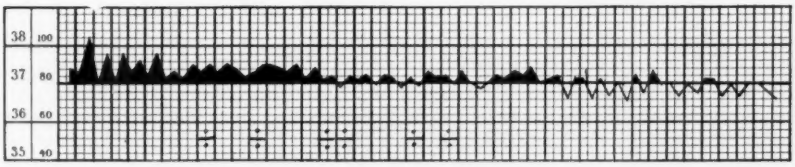


Chart 41.—Ulcer of small curvature in a woman, aged 49.

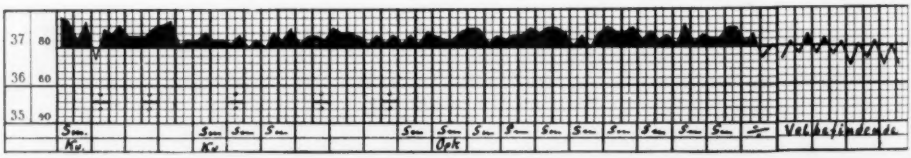


Chart 42.—Juxtapyloric ulcer in a woman, aged 48.

GASTRITIS

But how can this fever be explained? Faber [5] demonstrated that the postmortem smooth or atrophic mucous membrane by no means excludes the possibility of a pronounced gastritis during life, and I have begun to realize lately that the smooth ulcer found at autopsy really is a product of the postmortem effect of the gastric juice. Resections of the stomach particularly have furnished new information on this subject. Askanazy [6]

5. Faber: Acute and Chronic Gastritis, Kraus & Brugsch, 1921, vol. 5.

6. Askanazy: Bau u. Enst. d. chr. Magengegeschwürs, etc., Virchows Arch. f. path. Anat. **234**:111, 1921; **250**:370, 1924.

studied the fresh material from resections, and said that he was "astonished" the first time he looked at a recently removed and carefully prepared ulcer. Even as late as in 1919, Ashoff wrote that "any special deposits on the ulcer, exudates and necrotic masses, are practically absent," and that "the lack of inflammatory changes in the surrounding mucous membrane usually is conspicuous." The first contradictory statement, as far as I have been able to find out, came from Faber's department when G. Lange[7] (1910) mentioned some more or less marked inflammatory processes in about half of his material obtained

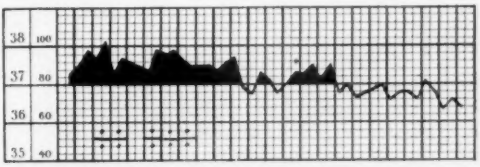


Chart 43.—Gastric ulcer in a woman, aged 24.

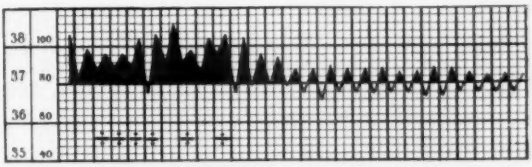


Chart 44.—Juxtapyloric ulcer in a man, aged 32.

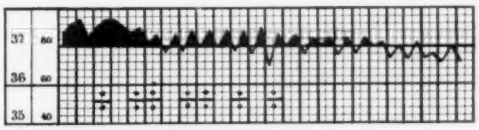


Chart 45.—Juxtapyloric ulcer in a woman, aged 27.

by resections. These, however, were mostly some very old ulcers. In 1921, Faber wrote, in his treatise on acute and chronic gastritis in Kraus and Brugsch's textbook, that the acute hematogenous gastritis which develops subsequent to infections does not show any macroscopic signs of gastritis, but that the microscopic examination reveals a marked round cell infiltration between the glands, usually associated with a marked development of lymphoid tissue. This process continues farther in a number of cases, forming small hemorrhagic erosions which can develop

7. Lange, G.: Studier over den kronische Gastritis, Inaug. Diss., Copenhagen, 1910.

into small ulcerations and result in an acute ulcerative gastritis. These erosions can give rise to hematemesis with more or less extensive inflammation of the mucous membrane, particularly around the ulcerations. "When the gastritis has persisted for some time, one can find that some of the small ulcerations extend farther out and particularly downward, forming a transition to true simple ulcers."

In 1921, Askanazy published a report on forty-four resected ulcers in which he "almost constantly" found even macroscopically four different layers: (1) a layer of exudate; (2) beneath this a 1.3 by 1.5 mm. thick opaque stratum, the "fibrinoid or diphtheroid necrotic zone"; (3) a layer of granulation tissue, often several millimeters in thickness, and (4) deepest, a layer of scar formation—at least in the older ulcers. The three first layers were of such a delicate structure that even the weakest stream of water at autopsy would remove them, not mentioning the postmortem digestion. It is not any wonder that the dissecting anatomist does not find these layers. In the fibrinoid zone Askanazy always found numerous leukocytes and often circumscribed "abscessartige Erweichungsherde." He considered the fibrinoid layer to be the product of an ever-developing, at least periodic, acute inflammation.

In the last two or three years Konjetzny [8] studied this resection material, and he came to the conclusion that a chronic gastritis is present with every ulcer of the stomach or duodenum, particularly in the region of the antrum, while the fundus usually does not show this condition. In forty-one resections for duodenal ulcer, he found gastritis and duodenitis present in 100 per cent, and in 54.5 per cent of these cases there were additional inflammatory defects of the mucous membrane outside the ulcers, i.e., erosions. He was strongly supported by Kalima,[9] who claimed that ulcers always were associated with a diffuse or focal gastritis and often with superficial ulcerations, and that this lesion was most marked in the pyloric area of the stomach and along the small curvature, while the other sections of the stomach were affected but slightly. There is no doubt that these erosions developed on bases of the gastritis and appeared in groups. The intermittent course of the gastrititis was probably the cause of the periodic appearance of the symptoms of ulcer. In this connection, Kalima mentioned that Faber had emphasized the fact that the uncomplicated chronic gastritis had a tendency toward an intermittent course. This helped to explain the characteristic exacerbations of peptic ulcer.

8. Konjetzny: Surgical Aspects of Chronic Gastritis, Arch. f. klin. Chir. **129**:139, 1924; Inflammatory Basis for Duodenal Ulcer, Deutsche Ztschr. f. Chir. **184**:85, 1924; Inflammatory Genesis of Ulcer of Stomach and Duodenum, Arch. f. Verdauungskr. **36**:189, 1925.

9. Kalima: Chronic Gastritis and Gastric and Duodenal Ulcers, Acta. chir. Scandinav. **58**:122, 1925.

Schmincke [10] found gastritis in 100 per cent of his patients with ulcers; von Haberer,[11] Heidenhein, Duschl,[12] Orator [13] and Finsterer came to similar results in reality, although their theoretical interpretation of these results were somewhat divergent. In 1926, Bohmansson [14] published the results of 185 resections in the hospital of Numeaa. Almost every section showed macroscopically a pronounced redness of the entire pyloric area, which was frequently swollen and edematous, while the fundus was much paler. This condition seemed to be constant in gastric ulcer and less constant in duodenal ulcer. Microscopic examination showed a constant increase of the plasma cells and polymorphonuclear leukocytes in the form of perivascular infiltration. The pus cells not infrequently accumulated as miliary abscesses. He considered the gastritis to be the primary lesion, and thought that the term "gastritis ulcerosa" would be correct. I reviewed his material in the hope of finding some recent and acute cases. However, it contained only six cases, but even these constantly showed considerable inflammatory changes in all the tissue layers with a macroscopic swelling and redness of the mucous membrane.

I will cite his case 63, because it is the only one in which the temperature is mentioned.

> The patient was admitted with a "slight" hematemesis and a temperature of 38.7 C. The fever lasted for one week. The symptoms in the stomach had been present for two months only. At the operation three ulcers were found above the angle. At least one of these was of recent date. The whole pyloric portion was considerably thickened. On macroscopic examination of the resected specimen the pyloric portion was found to be hardened, infiltrated, somewhat swollen and red, and there was a sharp line of demarcation between the normal mucous membrane of the fundic portion and the swollen mucous membrane of the pyloric portion. Microscopic examination showed a considerable plasma cell infiltration with occasional pus cells.

This case, then, was one of ulcer with a slight hemorrhage, considerable inflammation and fever—exactly the combination of symptoms that I take to be characteristic. Of course, to operate when an ulcer is in statu nascendi, so to speak, will always be a rare coincidence; but operations have been done at a still earlier stage of the ulcer formation,

---

10. Schmincke: Anatomische Befundean Ulcusmagen, München. med. Wchnschr., 1923, p. 1525.

11. Haberer: Zentralbl. f. Chir. **51**:67, 1924.

12. Duschl: Anatomy of Stomachs Predisposed to Ulcer, Deutsche Ztschr. f. Chir. **187**:55, 1924.

13. Orator: Gastric Ulcer, Mitt. a. d. Grenzgeb. d. Med. u. Chir. **35**:214, 1922; Beitr. z. Magenpath, Virchows Arch. f. path. Anat. **255**:639, 1925.

14. Bohmansson: Surgical Treatment of Gastric and Duodenal Ulcers, Acta chir. Scandinav. **60**:1, 1926.

namely, before the ulceration took place. One of Borgbjaerg's[15] (1922) two cases is of special interest. The operation did not reveal an ulcer, but a flat, purulent infiltration of the mucous membrane 2 cm. wide. On microscopic examination Melchior found considerable purulent changes, especially in the mucosa, with thickening of the submucosa and considerable diffuse cell infiltration, and a large portion of the gland crypts had undergone necrosis and liquefaction. It is more than probable that such a lesion is just about to become an ulcer, and it most likely will cause some fever.

More and more cases of this kind are being reported. Thus Konjetzny (1924) reported no less than nine analogous cases in which he performed operations. Most of the patients presented typical symptoms of ulcer for years—with hematemesis in four of them—and yet the operations did not reveal ulcer but chronic gastritis. Orator reported three cases of the same nature.

Thus, one may find every "ulcer symptom," periodicity, pains at night, hematemesis and even pyloric stenosis as in Borgbjærg's case, all present in chronic gastritis—a fact which Faber also has emphasized. One then naturally asks if, after all, the gastritis in gastric ulcer is not the lesion which gives the so-called symptoms of ulcer. The symptom that has been the subject of my investigation, namely, the fever, is reasonably referable to the gastritis. At any rate, it is evident from the quoted cases that the gastritis frequently is of such an inflammatory nature that the presence of fever seems reasonable.

COMMENT

When one looks at the whole matter from this point of view, the question is not how often the bleeding ulcers are associated with fever, but how often fever is connected with those lesions of the stomach from which ulcers develop. In 121 cases of manifest hemorrhages with fever, the diagnosis of ulcer was certain in fifty-nine patients; for in these patients the diagnosis was based on autopsy, on operation or on the presence of characteristic subjective symptoms, roentgen-ray observations, positive evidence in the functional stomach test and hemorrhage. Thirty-two additional patients showed characteristic signs of a lesion in the stomach, a characteristic anamnesis and hemorrhage—making a total of ninety-one patients, or 75 per cent. In twenty-two patients the hemorrhage occurred in direct connection with a period of dyspepsia; these together with those just mentioned make 113 patients, or 93.5 per cent, with symptoms in the stomach and hemorrhage. The lack of objective signs apart from the hemorrhage in the last twenty-two cases

15. Borgbjaerg: Ulcerative Gastritis, Arch. f. Verdauungskr. **30**:73, 1922.

was due to the fact that most of the lesions were acute, so that the characteristic signs had not had sufficient time to develop; and in several instances the lesion was cured before stomach tests could be made, as such examinations were carried out only when the patient had been free from symptoms for some time after the hemorrhage. In one of the remaining patients, the autopsy revealed a chronic gastritis of the same kind as that in Borgbjaerg's case. Finally, eight patients are left in which the only symptom was the hematemesis; in these cases the diagnosis was supported solely by the fact that no other cause of the hemorrhage could be found. If the doubtful cases are deducted, there were 113 cases (87 per cent) with fever in 130 cases of lesions of the stomach with manifest hemorrhage. If, however, I take into account only definite ulcers, fifty-nine of sixty-five cases, or 91 per cent, were febrile. These corrections in no way alter my first figures (87.5 per cent), because such corrections are not to be made in the groups "occult bleeding" and "no bleeding," as these groups comprise only objectively demonstrable ulcers. This shows that whether I merely take the definite ulcers into account, or I include all "stomach lesions with hemorrhage" (apart from cancer), I find fever present in nine tenths of all the patients.

BASAL METABOLISM

II. THE BASAL METABOLIC RATE IN RELATION TO SYMPTOMS AND SIGNS IN HYPERTHYROIDISM *

JAMES H. SMITH, M.D.
RICHMOND, VA.

The purpose of this paper is to compare the relative value in diagnosis of certain of the more classic symptoms and signs of hyperthyroidism. The criteria used are: (*a*) the bedside data furnished by these symptoms and signs themselves as compared with (*b*) the basal metabolic rate and (*c*) the pathologic examination of the resected thyroid gland when this material is available.

The method consists of arbitrarily assigning the values shown to the following six symptoms and signs: nervousness, 1; tremor, 2; loss of weight, 3; tachycardia, 4; exophthalmos, 5 and goiter, 6, making a total of 21. By this means a numerical index of symptoms is arrived at which can be readily represented graphically on a chart showing the relation of the numerical index to the basal metabolic rate.

Nervousness is a subjective symptom, vague in its definition, characteristic of a wide variety of diseases and not quantitively measurable.

Tremor is variable and except when typically fine, is not peculiar to hyperthyroidism.

The standard of loss of weight used in the study was 5 per cent or more of the recent normal weight of the patient.

By tachycardia is meant a pulse rate not falling below 90 under the conditions of the basal metabolic test.

The recognition of exophthalmos often involves the personal equation of the observer. If, however, a tendency is maintained to regard it absent unless positively present or plainly supported by other eye signs of hyperthyroidism, the sign is of high diagnostic significance.

The recognition of goiter is similarly involved. If the thyroid is appreciably enlarged, the degree of enlargement is of less significance as to the functional state than is the degree of vascular activity of the gland.

The cases studied number 147, taken consecutively without selection except to exclude those in which the patients had been recently treated with compound solution of iodine, by roentgen ray or by operation, presumably so as to modify the symptoms. The results are plotted in the chart. The symptom index is the base line, and the basal metabolic rate is the vertical.

---

* From the Medical Service of St. Luke's Hospital.

The great majority of those with a symptom index of 10 or less (102 cases) had a basal metabolic rate of less than plus 20, (one exception), and in only five of these 102 cases was the condition diagnosed as hyperthyroidism, though many of the patients had nontoxic goiter. On the other hand, all but four of the forty-five patients with an index of over 10 had a basal metabolic rate of more than plus 20, and

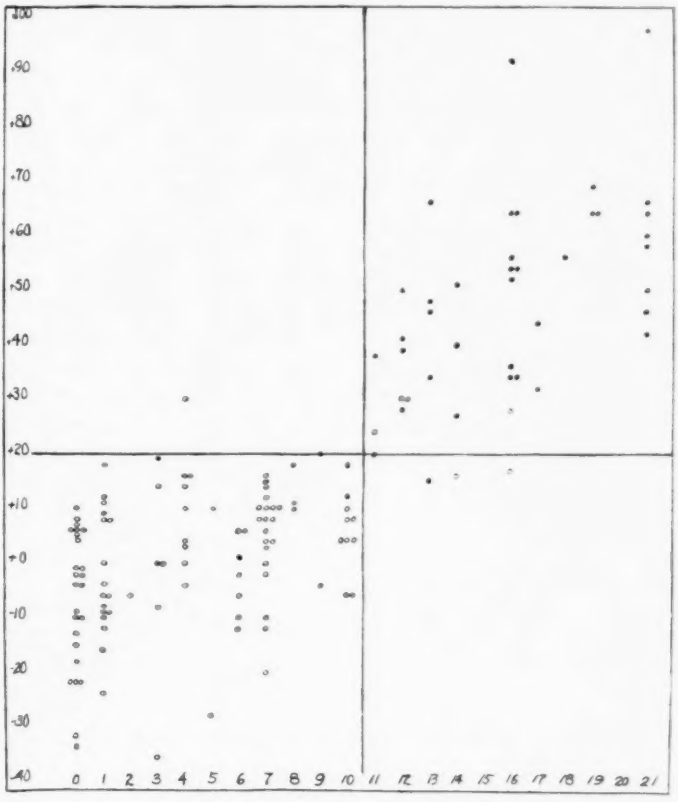


Chart showing relationship of the index of symptoms to the basal metabolic rate. The dark circles indicate the results for patients with exophthalmic goiter or toxic adenoma, and the light circles indicate the results for other subjects.

in all but four of these forty-one cases the condition was diagnosed as hyperthyroidism. The exceptions are briefly noted, and in some instances may be considered explained in the table.

The cases running according to rule fall in the southwest and northeast fields of the chart. With regard to the former there is

Data Relating to Cases Plotted in Chart Against the Rule, and to Case 11 in Which the Condition was Erroneously Diagnosed

Field	Case	Date	Name	Age	Sex	B. M. R.	Index	N.	Tr.	L.	Wt.	Tach.	Ex.	G.	Clinical Diagnosis	Thyroidectomy	Pathologic Report	Remarks
N. W.	41	2/ 8/26	E. F.	48	F	+30†	4	1	...		3	...	...	...	Chronic infectious tonsillitis	No	.....	Tonsils removed August, 1927; reported well Dec. 17, 1927
S. W.	1	12/16/25	P. P.	25	F	+19	3*	...	...		3	...	...	...				
							16‡	1	2		3	4	...	6	Duodenal ulcer, toxic adenoma	No	.....	No further record
	2	12/17/25	R. S.	16	F	+ 1	6	...	...		...	...	...	6	Nontoxic adenoma	Yes	Adenoma in mild exophthalmic goiter†	
	11	1/12/26	W. D.	27	M	+11	8	1	...		3	4	...	...	1/12/26, not made 3/6/26, probable toxic goiter†	Yes	Simple goiter or normal thyroid	
	68	3/16/26	H. F.	36	F	+20	9*	1	2		...	...	...	6				
							‡	1	2		?	...	?	6	Toxic adenoma	Yes	Toxic adenoma in exophthalmic goiter	
	129	9/18/26	N. J.	36	F	+12	10	1	...		3	...	...	6	Exophthalmic goiter	Yes	Borderline exophthalmic goiter	
S. E.	49	2/11/26	M. B.	37	F	+20	11	1	...		...	4	...	6	Psychosis	No	.....	Later a suicide
	48	2/12/26	L. H.	43	F	+15	13	...	...		3	4	...	6	Toxic adenoma	Yes	Toxic adenoma	"Much colloid, some calcium in the capsule and substance of adenoma"
	143	2/16/27	R. R.	30	F	+16	14	1	2		...	...	5†	6	Sympathicotonia	No	.....	Conspicuous difference in the two eyes
	76	3/26/26	M. W.	29	F	+17	16	1	2		3	4	...	6	Colloid goiter	Yes	Colloid goiter, thyroiditis	Taking compound solution of iodine for past six weeks
N. E.	57	3/ 1/26	S. W.	50	F	+24	11	1	...		...	4	...	6	Ovarian carcinoma	No	.....	No further records
	69	3/17/26	R. M.	24	F	+30†	12	1	2		3	...	...	6	Chronic infectious tonsillitis	No		
	136	10/ 6/26	C. C.	54	F	+30†	12	1	2		3	...	...	6	Nontoxic goiter	No	.....	1, 2 and 3 improved in next few weeks
	59	3/ 2/26	I. T.	20	F	+28	16	1	2		3	4	...	6	Chronic infectious tonsillitis	No	.....	12/17/27, reported still nervous and toxic thyroid suspected

† Considered erroneous. * Metabolism room record. ‡ Bedside record.

no subsequent record to indicate that any of the patients has subsequently become a recognized subject of toxic goiter. With regard to the northeast field, the condition in thirty-seven cases was diagnosed exophthalmic goiter or toxic adenoma. Most of these patients were subjected to operation and the thyroid tissue submitted for examination (thirty-one cases). The pathologic reports supported the clinical diagnosis in these thirty-one cases, whereas it did not in certain of the cases noted in the table.

The study suggests, as would be expected, that the diagnosis of hyperthyroidism approaches certainty as the index exceeds 10.

In the absence of exophthalmos and goiter (index 10 or less), hyperthyroidism was rarely found to exist even though nervousness, tremor, loss of weight and tachycardia were present.

When exophthalmos and goiter were present, other cardinal symptoms also occurred.

The absence of exophthalmos in toxic adenoma limits the total possibilities of the index in that condition, but the adenomatous goiter, if toxic, is usually associated with tachycardia and one or more of the other common symptoms.

The valuation suggested may occasionally serve as a useful check on erroneous acceptance or interpretation of the basal metabolism determination in the diagnosis of exophthalmic goiter and toxic thyroid adenoma.

THE EFFECT OF EMOTION ON BASAL METABOLISM *

HARRY L. SEGAL, M.D.

HERBERT F. BINSWANGER, M.D.
AND
SOLOMON STROUSE, M.D.
CHICAGO

The results obtained by two of us (Strouse and Binswanger) [1] from the therapeutic use of iodine in the treatment of patients for symptoms of the complex resembling hyperthyroidism without increased metabolism suggested the study of the relation between the nervous symptoms, metabolism and the use of iodine in hyperthyroidism.[2] To put this idea to experimental test involved a procedure which attempted to change the emotional state of a person and then to study the effect of such emotion on the metabolism. We believed that for our purpose in a general hospital, a simple procedure applicable to all classes of patients would give results of comparative value. Of course, we realized the improbability of evolving any standard test when dealing with emotion or of obtaining any constant emotional reaction to a given psychic stimulus. To this end we decided to study in operative cases the effect of the knowledge of an impending operation on the basal metabolic rate, pulse rate, blood pressure and subjective emotional state.

Three classes of patients were studied. The first consisted of the usual operative cases, the second of a group of patients with hyperthyroidism who had received the present day preoperative iodine therapy, and the third, patients with hyperthyroidism who had not received iodine or only insignificant amounts. After these patients had been in the hospital varying lengths of time, their basal metabolic rates were determined. Another metabolism test was done the morning before and the morning of operation, the patient having been informed of the time of operation the preceding evening. The pulse rate, blood pressure, respirations and emotional state were observed at the same time. In a few cases the technic was slightly altered in that the patient was informed on the morning of operation just previous to the metabolic reading.

* From the Thyroid Study Group and the Otto Baer Fund for Clinical Research of the Michael Reese Hospital.

1. Strouse, S., and Binswanger, H. F.: Symptom Complex Resembling Hyperthyroidism Without Increased Metabolism, J. A. M. A. **88**:161 (Jan. 15) 1927.

2. Hyperthyroidism is used throughout this paper as descriptive of a general group including all gradations from the typical exophthalmic goiter to the so-called adenomatous goiter with hyperthyroidism.

The basal metabolism test was performed at the bedside, the portable Benedict-Roth apparatus being used. Computations were made from the Aub-Dubois tables. In some cases one, and in some two, six-minute periods were run. Conditions of the test were always the same: the patient was in bed all night, and received nothing by mouth after midnight. Sedatives were not administered the evening before or the morning of operation. The pulse rate was taken during the breathing period, and the blood pressure and temperature by mouth immediately following. Respiratory quotients were not determined.

RESULTS

GROUP 1.—The first group consisted of twelve patients, eight males and four females, varying in age from 14 to 60 years. The basal metabolic rates were all within normal limits.

Only three of these patients showed any outward emotional manifestations on the morning of operation. The rate of metabolism of one of these rose 6.1 per cent (case 5); of the other two, one fell 4 per cent and one 13.4 per cent (cases 3 and 10). The pulse and blood pressure did not show any marked change. The remaining nine patients did not manifest demonstrable emotional reaction. Of these only one had an increase of 6.4 per cent, and this may be explained by an accompanying rise in temperature to 99.4 F. Either the others did not show any appreciable fluctuation or the metabolic rate decreased slightly. A constant relation did not exist between the pulse rate, blood pressure and metabolic rate. The respiration was not materially affected in any case.

GROUP 2.—The second group comprised twelve patients with hyperthyroidism who had received the present day preoperative treatment with iodine. In all of these the administration of compound solution of iodine had improved the nervous symptoms and had considerably lowered the basal metabolic rate. In most cases compound solution of iodine (Lugol's solution), 10 minims (0.6 cc.) three times a day, was administered for from six to twenty-five days. Two patients received 15 minims (0.92 cc.) three times a day, and in some an additional 30 minims (1.9 cc.) was given the night before operation. The patient in case 21 received syrup of hydriodic acid, 1 drachm (4 cc.) three times a day for fourteen days, followed by compound solution of iodine, 10 minims three times a day for thirteen days.

Of the twelve patients in this group (table 2), only five (cases 13, 17, 21, 22 and 24) showed outward emotional disturbances (nervousness and great anxiety). The metabolic rate in cases 13 and 17 remained practically the same the morning of operation, although the pulse in the former rose from 12 to 24 beats per minute. The

metabolic rates in cases 21, 22 and 24 increased approximately 6 per cent. The pulse rate rose in all of these, whereas the blood pressure varied.

Of the remaining seven patients, three (cases 16, 20 and 23) did not show appreciable change the morning of operation. In the last

TABLE 1.—*Data of Patients Not Having Thyroid Disease*

Case	Age and Sex	Relation to Operation*	Basal Metabolic Rate	Pulse	Respiration	Blood Pressure	Comment †
1	44 M	−1	−12.6	60–64	17	.....	Hernia
		0	−17.6	56–64	16	108/80	Informed of operation between 0 and 0^1
		0^1	−21.9	56	16	110/80	Told operation was to be performed
2	33 M	−1	+10.9	60–64	13	90/55	Hernia
		0	+ 4	72–76	14	.....	Informed of operation between 0 and 0^1
		0^1	+ 5	84	14	118/70	
3	60 M	−1	− 6.8	60	18	90/60	Duodenal ulcer, vomiting and emaciation
		0	− 8.7	56–60	16	90/64	Told he was to be operated on after 0 reading
		0^1	−12.7	56–60	16	106/96	Appeared angry, desired to see his wife
4	46 M	−1	+ 1	60	18	.....	Chronic osteomyelitis; eight previous operations
		0	− 6.3	60	17	104/80	
5	36 F	−1	− 9.7	88–96	19	.....	Chronic appendicitis; marked tremor
		0	− 3.6	88–96	19	114/80	Cried and was nervous morning of test
		+11	− 9.1	76–84	15	108/78	
6	52 M	−1	− 9.7	53	9	.....	Gastric ulcer
		0	− 8.1	52	9		
7	36 M	−1	− 3.8	48–52	15	90/45	Duodenal ulcer
		0	− 5.2	50	15	108/60	
8	46 F	−1	+ 9.1	52	16	118/70	Appendix; lagophthalmos
		0	+ 7.5	56–60	22	108/60	
9	44 M	−1	+ 3.8	71	26	100/70	Chronic intestinal obstruction
		0	+ 3	62–70	20	95/60	Coarse tremor
10	30 F	−3	+ 3.8	98–100	17	100/60	Retrocecal appendix
		−1	+ 5.2	80–92	18	104/70	
		0	− 8.2	88	20	110/70	Did not sleep most of night
11	37 M	−10	− 9.2	58	12	130/80	Cholecystotomy and appendectomy
		−7	− 2.6	52	12	124/70	
		0	−10	56–58	11	110/65	Up all night; pain in abdomen and shoulders
12	14 F	−2	− 3.4	68–72	10	114/58	Appendectomy; tremor, adolescent thyroid
		−1	− 4.7	68–72	9	108/60	
		0	+ 1.7	80	9	.....	Temperature, 99.4

* In this table and in tables 2 and 3, 0 indicates the morning of operation; 0^1 indicates that two tests were made on the day of operation, one before the patient was told of the operation and one after being told. Other numerals state number of days before or after operation.

†The patients were notified the night before of the operation except when otherwise stated. Outward manifestation of emotion did not occur unless indicated in this column.

two, the pulse rate and systolic pressure showed moderate rises. The metabolic rates in cases 15 and 19 fell approximately 8 per cent, without any changes in the pulse rate. The marked fall of 18.8 per cent in case 14 suggests the possibility of some error. The changes in metabolic rate, pulse rate and blood pressure did not present any parallelism.

GROUP 3.—As already stated, group 3 consisted of patients with hyperthyroidism who had not been iodinized. It is limited to only six

patients because of some untoward reactions which occurred. To obtain the effects of the mode of procedure adopted in the other two groups, these patients were likewise informed the night before that operation was to take place the next morning. But after the metabolism test was made that morning, actual operation did not follow. They were then put on the present day preoperative course of iodine. Four of

TABLE 2.—*Data of Patients with Thyroid Disease Treated with Compound Solution of Iodine*

Case	Age and Sex	Relation to Operation	Basal Metabolic Rate	Pulse	Respiration	Blood Pressure	Amount of Iodine Received, Cc.	Comment
13	40 F	−7	+35.5	100	26	120/ 50	32	Nervous
		−1	+30.2	92	21			
		0	+31.6	104-114	29			
14	37 F	−1	+47.4	84- 98	11	108/ 50	24	
		0	+28.7	90- 94	10	110/ 60	..	Did not sleep well due to noise next door
15	37 M	−7	+31.8	108	13	.....	29	
		−1	+29.9	76	12	100/ 50		
		0	+22.4	78- 90	10	100/ 55		
16	22 F	−19	+56	124	24	.....	40	
		−1	+42.4	104	18			
		0	+39.7	.....	21	138/ 62		
17	40 F	−1	+35.1	108-112	13	130/ 70	42	
		0	+36.3	108-110	12	118/ 40	..	Great anxiety
18	48 F	−19	+61.7	116	21	144/ 80	13	
		−1	+39.2	96-104	20			
		0	+47.7	100-108	19	130/ 80	..	Temperature, 99
		+3	+42.7	88	18	110/ 60		
19	32 F	−11	+53.7	104	16	98/ 60	18	
		−1	+23.7	80- 88	15			
		0	+14.9	84	16	110/ 60		
20	29 F	−28	+40.8	132	15	.....	34	
		−1	+19	100-104	16	100/ 40		
		0	+19.7	120-130	15	125/ 49		
21	43 F	−35	+56.7	.....	..	148/ 96	28	From April 19 to May 3, 1 drachm of syrup of hydriodic acid was given three times a day
		−12	+31.1	140-152	20	190/110		
		−1	+29.1	114	22	180/104		
		0	+35.4	120-124	22	184/106	..	Worried a great deal
22	32 F	−1	+29.3	88- 94	21	104/ 60	22	
		0	+34.5	104-114	17	124/ 0	..	Showed anxiety
23	34 M	−1	+32.1	98- 98	24	138/ 70	31	
		0	+33.3	120-128	25	150/ 70	..	Temperature, 99.2
24	33 F	−1	+37.6	93- 94	24	118/ 62	30	
		0	+44.3	110-114	24	118/ 50	..	Temperature, 99; excited

these patients are also included in group 2, thus affording us the opportunity of studying them before and after iodine therapy.

The results obtained are discussed individually. The metabolic rate in case 14 rose from + 43.1 per cent two days before operation to + 77.7 per cent the morning of operation. The pulse rate and blood pressure remained constant. The metabolic rate in case 23 increased from + 50.7 per cent to + 75.8 per cent within a few minutes. The pulse rate and systolic blood pressure ascended slightly. This patient

was the only one of this group who had received any compound solution of iodine before this experiment. He had taken five drops three times a day for two weeks, and the metabolic tests were done seven days after iodine had been discontinued. In case 24 the metabolic rate the day before operation was + 72.6 per cent, and the morning of supposed operation it was + 97.2 per cent. Here again the pulse rate remained practically unchanged. The following day the rate of metabolism returned almost to its previous level. In case 25, the morning before supposed operation the metabolic rate was + 47.6 and the morning of operation, + 66.5 per cent. The pulse rate and blood pressure are of

TABLE 3.—*Data of Patients with Hyperthyroidism Who Did Not Receive Compound Solution of Iodine*

Case	Age and Sex	Relation to Operation	Basal Metabolic Rate	Pulse	Respiration	Blood Pressure	Temperature	Comment
14	37 F	−2	+43.1	104	19	130/70		
		0	+77.7	100-106	15	134/70		
23	34 M	0	+50.7	110-130	27	130/60	....	Informed of operation after reading of 0
				108-136	32			
		0[1]	+75.8	124-132	29	146/62		
24	32 F	−5	+77.9	116	29			
		−1	+72.6	124				
		0	+97.2	120-132	20	130/ 0	....	Greatly excited
		+1	+79.9	124	24			
		+2	+83.6	124	22			
25	58 M	−5	+38.4	100-104	14	112/60	98.6	
		−1	+47.6	Irreg.	14	156/40	98	
		0	+66.5	100-112	15	96/50	98	
		+1	+35.6	108-114	14	120/68	98	
22	32 F	−3	+40.9					
		−1	+41.6	114-116	18	126/60	99	
		0	+53.8	.....	19	70/80	99	Greatly excited
		+1	+52.5	120	19	138/60	99	
26	44 F	−1	+53.9	114-122	20	140/80	98.6	
		0	+182	116	21	150/50	98.6	
			+270	150	17	164/70	100.2[2]	Metabolism test repeated one hour later
		+1	+63.4	108-112	20	140/60	98	

[1] Rectally.

doubtful value, as fibrillation was present. In case 22 occurred the least increase, which was 12.2 per cent. On the following morning, the rate of metabolism had not returned to the level found before operation. The pulse rate was not recorded the morning operation was performed. The systolic blood pressure rose 44 mm. and the diastolic, 20 mm. This patient and the one in case 24 both showed marked excitability on the morning of operation. In case 22, the maintenance of the same metabolic rate as that found the morning following operation is possibly due to the excitement brought on by the woman's reluctance in having this metabolic test performed. She had been instructed that no more tests were to be done.

Case 26 is remarkable in the reaction that occurred. On the morning before operation, the rate of metabolism was + 53.9 per cent and within the range of previous determinations. On the morning of operation it reached the high level of + 182 per cent, although the pulse rate remained about the same as that of the previous morning. Immediately following the metabolism test, the patient went into a state simulating acute thyroid intoxication. The pulse rate rose to 160, and the temperature to 100.2 rectally. Morphine sulphate, $\frac{1}{6}$ grain (11 mg.) was administered hypodermically, and the metabolism test was repeated about one hour later. At this time the metabolic rate was + 270 per cent, the pulse rate 150 and the temperature, 100.2 rectally. By afternoon the patient seemed to have made a good recovery. The following morning, the basal metabolic rate was + 63.4 per cent, the pulse rate 110, and the temperature was normal.

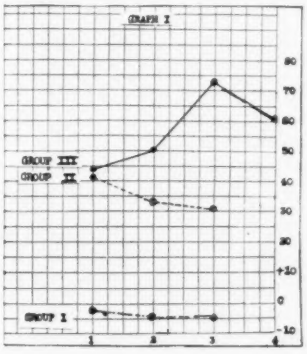


Figure 1

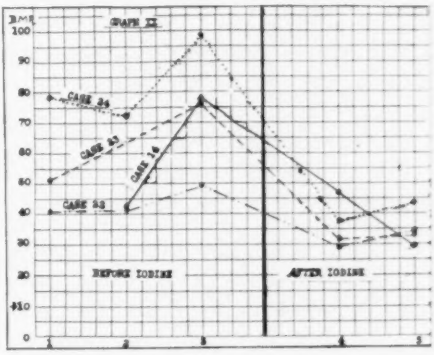


Figure 2

Graph I represents the average changes in metabolism in the various groups, while graph II shows the difference in metabolic rate obtained in the same patients by the same procedure after iodine therapy.

The average changes in metabolism in the various groups are represented in graph I of the accompanying chart. Graph II shows the difference in metabolic rate obtained in the same patients by the same procedure before and after iodine therapy.

COMMENT

In the literature various methods have been employed to demonstrate the effect of emotional reactions on metabolism. Necessarily, numerous factors come into play which make results difficult to interpret. Grafe and Mayer [3] performed a series of experiments on hypnotized

3. Grafe, E., and Mayer, L.: Ueber den Einfluss der Affekte auf den Gesamtstoffwechsel, Ztschr. f. d. ges. Neurol. u. Psychiat. **86**:247, 1923.

persons, suggesting various calamities such as death of relatives, amputation of arms, etc. In nine such tests, there was an increase in metabolic rate ranging from 5 to 25 per cent. In four experiments no change or only a slight lowering of the rate occurred. From this the authors concluded that emotion may cause a definite increase in metabolism.

Ziegler and Levine,[4] making tests on psychasthenic war veterans, found a marked rise in the metabolism as the result of emotion in eleven cases; in three they found a fall, and in one not any change. They produced emotional disturbance during the breathing periods, by having the veterans think of a disagreeable experience in the army. Crile [5] stated that the metabolic rate falls in rabbits badly frightened by dogs. Landis [6] reviewed the literature concerning the relationship between the metabolic rate and the emotional state of psychotic persons and found that an altered or emotional state does not necessarily affect the metabolic rate. In his experiments, anticipation of strong electrical stimulation raised the metabolism in three persons tested, 6, 17 and 37 per cent. He stated that emotional disturbance per se does not always produce the same change in the metabolic rate.

The question arises whether our procedure affected the emotional state. In all our patients outward indications of emotional reactions were not noted, but the significant fact is that the same mode of procedure in different groups of persons resulted in similar effects on the basal metabolism in two groups, and a totally different reaction in the third group. These results occurred whether or not subjective manifestations of emotional reactions were present. The basal metabolic rate of patients not having thyroid disease was not heightened by this procedure; the caloric output of the majority of patients with thyroid disease whose condition had been stabilized by iodine therapy was likewise not affected. In some, a slight rise occurred. The increase resulted in those patients with hyperthyroidism who had not received the present day iodine therapy.

With a similar procedure in patients with thyroid disease who had not received iodine, Segall and Means [7] obtained a rise in the metabolic rate the morning of operation, but the average increase in their experiment was from 1 to 6 per cent. In our six cases the increase ranged

4. Ziegler, A. M., and Levine, B. S.: The Influence of Emotional Reactions in Basal Metabolism, Am. J. M. Sc. **169**:68, 1925.

5. Crile, G. W.: The Thyroid Gland, Philadelphia, W. B. Saunders Company, 1922.

6. Landis, C.: Studies of Emotional Reactions—Metabolic Rate, Am. J. Physiol. **74**:188, 1925.

7. Segall, H. N., and Means, J. H.: The Immediate Effect of Subtotal Thyroidectomy in Toxic Goiter, Arch. Surg. **8**:176 (Jan.) 1924.

from 12.2 to 24.6 per cent, the patient who had a profound reaction not being considered. It is possible that this difference in results is due to the fact that Segall and Means' patients received morphine sulphate, ¼ grain (16 mg.) hypodermically previous to the metabolism test.

What is the mechanism that produces the increase in metabolic rate in these patients with thyroid disease? Grafe [8] believed that the rise of caloric output following emotion is caused by a general alteration in the organism as a result of stimuli from centers in the brain passing out to the periphery, chiefly by means of the sympathetic nervous system and also by some increase in the metabolism of the brain itself. Aub [8] thought that the effect is due to epinephrine, the point of action being a direct one, in that it influences the metabolism by affecting the peripheral muscle tissue. Segall and Means also considered it an epinephrine response. The latter views fit in with Cannon's theory [9] of epinephrine reaction to fright and fear. Our results in the patients of group 3 likewise suggest an increased production of epinephrine as the cause of the metabolic change, for in three of the four cases studied before and after the administration of iodine, the caloric output had dropped the following day. This could not be consistent with a thyroxin reaction, because thyroxin produces a reaction lasting days or even months. The increased heat production due to epinephrine is immediate and transient.

We are unable to state why such a marked reaction should occur in patients with hyperthyroidism who have not received compound solution of iodine as compared with those who have received sufficient iodine. Naturally this brings up the old question as to the mechanism that causes iodine to reduce, to a certain extent, the nervous symptoms and metabolic rate in hyperthyroidism. We cannot say whether it fits in with Plummer's [10] idea or the latest mechanical one of Marine,[11] who suggests that the enlargement of the vesicles produced by the increased colloid in the regression of the hyperplasia compresses the lymphatics and capillaries and thus lessens the absorption of thyroxin. Perhaps those patients with thyroid disease who had received iodine and who

8. Aub, J. C.: The Relations of Internal Secretion to Metabolism, J. A. M. A. **79**:95 (July 8) 1922.

9. Cannon, W. B.: Bodily Changes in Pain, Hunger, Fear and Rage, New York, D. Appleton and Company, 1915.

10. Plummer, H. S.: Results of Administering Iodine to Patients Having Exophthalmic Goiter, Society Proceedings, J. A. M. A. **80**:1955 (June 30) 1923.

11. Marine, D.; Deutsch, M., and Cipra, A.: Effect of Large Doses of Iodine in Heat Production in Rabbits, Proc. Soc. Exper. Biol. and Med. **24**:657, 1927.

still had a slightly increased metabolic rate the morning of operation were markedly hyperplastic and sufficient iodine had not been administered.

SUMMARY

1. The effects of the thought of impending operation on basal metabolic rate, blood pressure and pulse rate were studied in three groups of cases.

(*a*). A constant effect on the rate of metabolism was not seen in group 1, which consisted of patients of various types of nervous stability with a normal rate of metabolism.

(*b*). In group 2, which was made up of patients with hyperthyroidism who had received iodine according to present day preoperative routine, a marked rise in metabolic rate did not occur the day of operation.

(*c*). Group 3 was comprised of persons with hyperthyroidism who had not had iodine, as in group 2. In these patients a marked increase in the basal metabolic rate resulted the morning of supposed operation.

2. A practical point for consideration is the possibility of using the foregoing procedure as an index of complete or incomplete iodinization. A rise of the metabolic rate the morning of operation might indicate that an insufficient amount of iodine had been given.

SECOND INFECTION IN SYPHILIS

ITS RELATION TO THE TIME OF TREATMENT OF THE FIRST INFECTION *

CHARLES R. L. HALLEY, M.D.
WASHINGTON, D. C.
AND
HARRY WASSERMAN, M.D.
BALTIMORE

It has long been recognized that second infections in syphilis in man are not common; indeed, prior to the discovery of spirochetes and the introduction of arsphenamine, a comparatively small number of supposed instances had been reported, and there was considerable discussion as to their actual occurrence. Ricord and Fournier stated that they had never observed a satisfactory example, whereas in 1895 Hutchinson reported fifty-four "reinfections," only a few of which his son later was willing to accept.

When the diagnosis of syphilis rested on clinical grounds alone, the recognition of the occurrence of second infection with this disease was admittedly difficult and frequently open to question. Many of the instances reported prior to 1910 may have been and doubtless were true examples of second infection, but since the diagnosis rests entirely on clinical grounds, the evidence is hardly acceptable according to present standards. With the discovery of the causative agent of the disease, it was possible to place the identification of a second infection on a firmer footing, for now exact proof of the syphilitic nature of the suspected lesion can be adduced. In 1914, Benario collected from the literature ninety-six reported cases of "reinfections," in which the patients had first been treated with the recently introduced arsphenamine or with arsphenamine and mercury. He was concerned mainly with the superior curative properties of arsphenamine, as evidenced by the great number of "reinfections" reported within a few years. It is now generally accepted that second infections do occur, which may and usually do behave in all respects like first infections.

THE PROBLEM

As a result of his experiments on apes, Neisser came to the following conclusions in regard to syphilitic infection: radical cure of the disease can be effected by appropriate treatment; treated animals can be infected

* From the Department of Medicine of the Johns Hopkins Medical School, Baltimore.

a second time under certain conditions; a successful second inoculation indicates the elimination of the first infection; failure of the second inoculation indicates the presence of a resistant state (immunity); the presence of this resistant state depends on the persistence of the first infection; without a persistent infection, there is no resistant state, and hence the demonstration that any particular treated animal is resistant to a second inoculation indicates the failure of treatment to bring about cure of the first infection in that animal. Until recently these conclusions have dominated the conception of acquired immunity in syphilis, both in man and animals. However, fresh evidence of an experimental nature has appeared which questions the validity of the idea that immunity in this disease is necessarily dependent on the presence of spirochetes in the tissues.

Brown and Pearce showed that in rabbits early nonsterilizing treatment (eighteen days after inoculation) rendered the animals susceptible to a second inoculation six days later with a homologous strain of the syphilitic virus. Kolle was the first to show experimentally that the time at which treatment is begun in the course of syphilitic infection exerts an important influence on the reaction to a second inoculation with the homologous strain of spirochetes. This investigator found that if syphilitic rabbits were treated within forty-five days after inoculation, they could almost invariably be infected a second time; whereas, if treatment were postponed until ninety days or more after the first inoculation, they were almost always resistant to a second inoculation with homologous strains of spirochetes. On the basis of Neisser's generalizations, Kolle concluded that the successful second infection of the rabbits treated early indicated that they had been cured, but that the rabbits treated late had not been cured, since they were refractory to a second inoculation. The experimental results of Kolle have been confirmed by Frei, Adachi and Chesney and Kemp. The last named workers found in addition that, no matter whether treatment was begun before the forty-fifth day or postponed until after the ninetieth day, it was apparently effective in sterilizing the lymph nodes and internal organs of the rabbits. Their experiments suggested that the specific resistance which develops during the course of syphilitic infection may persist after the infection has been eliminated, and hence may not necessarily be dependent for its continued existence on the presence of spirochetes in the host. It is obvious that this conception of acquired immunity in syphilis is at odds with the conception formed by Neisser and generally held since his day.[1]

1. For a complete discussion of the question of immunity and resistance in syphilis, see "Immunity in Syphilis" by A. M. Chesney.

If, as Neisser concluded, acquired immunity to syphilis is dependent on the persistence of the original infection, and if the present intensive method of treatment, regardless of the time at which it is begun, can bring about a complete cure, there should have occurred by now many second infections of syphilis in patients who came under treatment for the first time late in the course of the disease, provided always that many persons who have had syphilis are subsequently exposed to infection. Since 1910, many syphilitic patients have been given intensive treatment comparatively late in the course of the disease. Hence it is now possible to determine the relation of the time of treatment of patients with first infections to the incidence of second infections, and, as a corollary, to ascertain the proportion of second infections occurring in patients in whom treatment was begun late in the course of the disease. Such is our purpose in this communication.

SELECTION AND CRITERIA OF REPORTED INSTANCES OF SECOND INFECTION

We have reviewed the case reports in the literature since 1910 of examples of "reinfection," "superinfection" and "second infection," the last of which terms we prefer since it implies nothing in regard to the presence or absence of the first infection. Unfortunately, a few of these reports were in unavailable journals and do not appear in this collection, nor have we been able satisfactorily to tabulate many examples reported as a part of general studies of the results of treatment. Altogether we have reviewed the reports of cases of 676 patients with supposed second infections, to which are added eight instances from the syphilis clinic of the Johns Hopkins Hospital, which have not hitherto been reported in detail.

We have sought to determine whether or not all these instances could be regarded as examples of second syphilitic infection in accordance with criteria which we have adopted for the recognition of such a condition. We have two such criteria:

1. There must be proof that the patient had syphilis prior to the occurrence of the suspected second infection, and this proof must rest on the demonstration of spirochetes in a lesion or the occurrence of a positive Wassermann reaction in the blood serum, and not on clinical judgment alone.

2. After an interval following antisyphilitic treatment and at a site other than that of the primary lesion of the first infection, there must develop a lesion with the characteristics of a chancre in which spirochetes can be demonstrated.

These criteria are not as rigid as those formulated by Stokes, but we consider that they are adequate for the establishment of the existence

of a second infection. They are not based on clinical diagnosis alone. It would be more convincing if every patient suspected of having a second infection could have been allowed to go without treatment for a period of time sufficient to permit him to develop signs of secondary syphilis. Before the discovery of the causative agent of syphilis such a procedure was necessary to establish the validity of a second infection, but in our opinion that is no longer necessary, nor is it even desirable from the point of view of the patient himself or of society in general. It may not be amiss to point out that if too rigid criteria are adopted, statistical study of second infections in human syphilis will never be possible unless there is great improvement in the manner of reporting such instances.

In a few instances, we have been unable to adhere strictly to the criteria of a second infection, so far as the location of the second chancre was concerned, although such examples have been included in this study, because some of the reports fail to state the precise location of the suspected primary lesion of the second infection in relation to the site of the original chancre. This is, of course, regrettable but could not be helped. It will be obviated if in the future those reporting instances of suspected second infection will be more explicit on this point.

When the 676 case reports were studied in the light of the criteria already outlined, it became necessary to reject 447, either because the data were insufficient for the purposes of this study or because the supposed instances did not fulfil the proposed criteria. The remaining 229, which were deemed acceptable, together with the eight from this clinic, were studied with reference to the time at which treatment was begun during the course of the first infection, and also with reference to the interval between the beginning of the treatment and the onset of manifestations of the second infection. The data obtained from this study are presented in table 1 in summarized form.

In group A of this table are presented all those patients in whom the interval between the beginning of the first treatment and the second infection (or the appearance of the lesion of the second infection) was more than a year, and in group B, those patients in whom this interval was less than a year. This distinction has been made because it is thought that in treated syphilitic patients, relapses which take the form of primary or secondary lesions, and hence might be mistaken for second infections, are most apt to occur within the first year of observation. If this is true, those patients designated as group A are more likely to be true instances of second infection than those in group B.

Consideration of this table shows that of the 237 reported instances regarded as acceptable, 232, or 97.8 per cent of the patients received

active treatment early in the course of the first infection, that is to say, during the primary stage of the condition or before the secondary lesions had disappeared. Of these, 165 were treated in the primary and 67 in the secondary stage. There were only 4 patients in whom treatment was begun in the latent stage, and in whom there was subsequently good ground for believing that a second infection had occurred. There was one patient with undoubted evidence of congenital syphilis who acquired a second infection. Not a single instance could be found of

TABLE 1.—*Patients with Second Infection Showing Stage of First Infection at Time of Treatment*

Stage	Group A	Group B	Total A and B	Per Cent
Primary duration and serology unknown.....	7	13	20	8.4
Primary seronegative; duration unknown.....	21	16	37	15.6
Primary seropositive; duration unknown.....	23	17	40	16.8
Primary duration known; serology unknown..	9	2	11	4.6
Primary duration known; serology negative..	20	13	33	13.9
Primary duration known; serology positive....	16	8	24	10.1
Total Primary	96	69	165	69.4
Secondary duration known.....	9	4	13	5.4
Secondary duration unknown.....	34	20	54	22.7
Total Secondary	43	24	67	28.1
Total Primary and Secondary.....	139	93	232	97.5
Latent	4	0	4	1.6
Congenital	1	0	1	0.4
	144	93	237	100.0

TABLE 2.—*Patients with Second Infection Showing Duration of First Infection Before Treatment*

Weeks	1-2	2-3	3-4	4-5	5-6	6-7	7-8	8-9	9-10	10-11	11-12	12-13	13-14	14-15	15-16
Primary-serology unknown	.	1	2	4	1	2	1	.	.	.	.	.	.	.	.
Primary seronegative	3	2	10	10	2	4	1	.	1	.	.	.	.	.	.
Primary seropositive	3	1	2	3	1	5	6	2	2	.	1	.	.	.	.
Secondary	.	.	1	1	.	1	1	1	.	.	1	5	.	1	1
Total	6	4	15	18	4	12	9	3	3	.	2	5	.	1	1
(Eighty-three patients)															

a second infection in a patient whose treatment was started when tertiary lesions were present.

More precise information as to the duration of the first infection before treatment was begun, reckoned from the date of exposure, was available in eighty-three instances. This information is summarized in table 2.

This table shows clearly that in man the number of instances of second infection of syphilis diminishes as the interval between the onset of the infection and the initiation of treatment increases. The same phenomenon also occurs in experimental syphilis in rabbits, pro-

vided that a homologous strain of spirochetes is used for the second inoculation. The parallelism of the conditions obtaining in man and in the rabbit is pointed out more clearly in table 3.

In each species there is observed a progressive diminution in the incidence of second infections when the time elapsing between the onset of the disease and the institution of treatment increases.

TREATMENT

All the patients included in this series were treated during the first infection with arsphenamine, either alone or in combination with other drugs, except that one patient received mercury only, another a proprietary arsenical product only, and a third bismuth only.

TABLE 3.—*Second Infections in Rabbits and Man*

	Duration of First Infection Before Treatment								
	To Forty-Six Days			Forty-Six to Ninety-One Days			Ninety-One + Days		
	Total Number	Positive	Per Cent	Total Number	Positive	Per Cent	Total Number	Positive	Per Cent
Second inoculations in rabbits *	85	73	85.8	95	34	35.7	148	7	4.7
Second infections in man	to Forty-three Days Forty-six Patients			Forty-three to Ninety-Two Days Thirty-three Patients			Ninety-two + Days Two Patients		

* In obtaining data for rabbits, material has been taken from papers by the following investigators: Kolle, Chesney and Kemp, Chesney, Halley and Kemp, and Adachi.

THE RARITY OF SECOND INFECTIONS IN WOMEN

It is striking that of the 237 instances of second infection included in this paper, only 8, or 3.3 per cent, occurred in women. Several possible explanations for this comparatively low incidence among women in our series suggest themselves. It can scarcely be due to the relative incidence of syphilis in the two sexes, for, while the disease is probably more common in men, it is not twenty-eight times as frequent as in women. A partial explanation may be found in the well known tendency of syphilis to run a silent course in women, often being detected only by the occurrence of a positive blood Wassermann reaction. Such patients, numerous in any large syphilis clinic, are apt to come under treatment comparatively late in the course of the infection and, as our study has already shown, the incidence of second infections under these circumstances is extremely low. Possibly, also, the infrequency with which careful vaginal examinations are made in women in whom a positive Wassermann reaction is detected may play an important rôle in that instances of second infection with chancres on the internal genitalia are overlooked.

RECURRENT LESIONS AND THIRD INFECTIONS

There were recurrent lesions, usually of secondary type, during the first infection in seventeen patients, all of whom were further treated. In compiling our tables, we classed these according to the stage of the recurrent lesions. These patients show that even with recurrent lesions, immunity may not develop to an extent sufficient to prevent a subsequent second infection.

There are in this series eight patients in whom third infections with syphilis occurred, in accordance with the criteria of this study. They afford evidence that third infections actually do occur, and further support the conclusion that if the patient is treated early, little if any immunity against subsequent infection develops.

SECOND INFECTIONS IN PATIENTS WITH VARIOUS TYPES OF SYPHILIS

Second Infections in Patients with Congenital Syphilis.—Only the report by Tashiro of the case of a 25 year old man has been accepted as an instance of second infection occurring in a patient with stigmas of congenital syphilis. Other supposed examples have been reported by Arning, Doucy and Joltrain, Gaston, Gaucher, Gougerot and Guggenheim (two patients), Goizet, Hudelo and Jolivet, Roederer and Camus, Stern, and Suggett (two patients). Arning's case was considered doubtful, because it was felt that the diagnosis of congenital syphilis was made on inadequate evidence; the patient, who had hutchinsonian teeth, developed on the lower lip a chancre which contained spirochetes. It seems questionable that the occurrence of hutchinsonian teeth alone (with no report as to the Wassermann reaction) can be accepted as certain evidence of a preexisting congenital syphilis. The other cases were deemed unacceptable, because the diagnosis was uncertain as regards either the congenital or the acquired infection.

Second Infections in Patients with Evidence of Syphilis of the Central Nervous System.—The following authors have reported patients who are supposed to have acquired a second infection with, either previously or concomitantly, suggestive evidence of syphilis of the central nervous system; Brandt, Brandweiner, Fiocco, Friedländer (two patients), Gennerich and Zimmern, Lambrior (three patients), Pöhlman, Stümpke, and Zieler. Not one of these cases has been deemed acceptable for this study, because the diagnosis of one or the other of the two conditions is open to question, although in one of Friedländer's patients a diagnosis of tabes (without a report of the spinal fluid) had been made several years before the patient developed a penile lesion which contained spirochetes.

Second Infections in Patients with Cardiovascular Syphilis.—Possible or certain recently acquired syphilitic infection in patients having more or less definite evidence of aortitis or aneurysm, resulting from a supposed previous syphilitic infection, has been reported by Conrad, Fischer, Oro, and Zak, but after critical study not one of these cases has been considered acceptable for this paper.

COMMENT

This review of the instances reported in the literature since 1910 as examples of second infection with syphilis discloses that many of these must be regarded as doubtful, in the absence of more precise data. Of the 676 case reports studied, only 229 proved wholly acceptable according to the standards outlined. If these represent true instances of second infection in syphilis, then certain facts can be deduced from this study.

First, a remarkable parallelism is apparent, so far as the relation of the time of treatment of the first infection is concerned, between the results of reinoculation experiments in treated syphilitic rabbits and the occurrence of second infections in human beings treated for syphilis. In each species there is observed a lessened tendency toward the occurrence of second infections when a longer interval ensues between the occurrence of the infection and the beginning of treatment.

Second, in the overwhelming majority of instances regarded as second infections (97.8 per cent), the patients came under treatment for their first infection during the early stage of the disease, that is to say, before the period of secondary manifestations had elapsed. A slightly greater number of patients were first treated during the seronegative primary stage than during the seropositive primary stage (70 as compared with 64). A much greater number were first treated during the primary stage than during the secondary stage (165 as compared with 67). These differences suggest an increasing resistance on the part of the patient, in the absence of any precise data as to the relative frequency of primary and secondary syphilis in patients presenting themselves for treatment at a syphilis clinic. It is almost impossible to obtain any accurate figures as to the percentage of patients first seen in the seronegative or seropositive primary and early secondary stages, since these vary greatly according to the type of clinic (e. g., Gennerich and Zimmern, working with patients in the German navy, see the lesions early), the character of the patients, and other factors; but on the average, the number of patients in the primary stage who seek admission to a clinic will probably be considerably less than that in the secondary stage, while of those with primary lesions the greater number will probably be seen for the first time when the Wassermann reaction has become positive. Yet there were over 2½ times as many

patients with second infections in whom treatment was begun during the primary stage as there were those in whom treatment was begun after secondary lesions had appeared. The almost complete absence of second infections in patients who had latent syphilis at the time treatment was begun is striking, as well as the complete absence from this series of patients with tertiary lesions. Is this difference in the percentage of second infections in patients with syphilis who are treated early and those who are treated late to be explained on the basis of a greater number of cases of syphilis in which the patients come under treatment in the early stage of the disease than later?

A survey, shortly to be published, of all patients admitted to this clinic during seven years from 1920 to 1926 inclusive, reveals that of 8,064 new patients, 1,898 were first treated during the primary and secondary stages, that is, early; 3,895 were treated during the late stages; in the remaining number, the condition was undiagnosed or diagnosed nonsyphilitic, or the stage of the disease was not determined because of insufficient observation. The ratio of patients with early and late syphilis (1,898 as compared with 3,895) is thus almost exactly 1:2. Yet, as revealed by this paper, second infections occur in patients treated early as compared to those treated late in the ratio of 232:5 or 46:1. In other words, approximately twice as many patients are treated for the first time late in the course of the disease as are those treated early, yet second infections occur forty-six times more often in the latter than in the former group.

Is the difference to be explained on the assumption that postponement of treatment until late in the course of the disease fails to bring about radical cure and hence leaves the person still infected and perhaps immune to a second infection? It is almost universally admitted that it is much more difficult to cure patients who have syphilis when treatment is begun late than when it is begun early, especially if extensive disease of the internal organs has developed; but it is at least conceivable that patients with a long-standing infection without such extensive visceral involvement may be cured even if treatment is begun late. At present we do not know of any adequate clinical studies on this point.

Another possibility that might explain the difference in the percentage of second infections in patients treated early, as opposed to those treated late, is that patients who have reached the late stage of syphilis before being treated are not so apt to be exposed to second infections as are those who have come under treatment early in the course of the disease. The former are apt to be older, and their social relationships different (marriage, better economic circumstances) from those of the latter and of a sort making for less exposure to

syphilitic infection. While this explanation can be neither dismissed nor proved, it has much less weight when considered in connection with those races in which syphilis is most prevalent, for in them exposure to syphilis begins relatively early in adolescence and often continues in spite of matrimony.

It is clear that the great infrequency of second infections of syphilis in patients coming under treatment late in the course of their first infection can also be explained on the basis of an acquired immunity which persists in the absence of the first infection, that is, after treatment has effected a cure. There is some experimental basis for this view. Whether or not it is the correct explanation is impossible to say, but this much can be said, that if there were no such thing as acquired immunity to syphilitic infection persisting in the absence of the infection, and if modern treatment were effective in eradicating the disease, then, assuming that repeated exposure to infection occurs, one should be able to assemble a significant series of instances of second infection with syphilis in which treatment for the first infection was not undertaken until late in the course of the disease. It has not proved possible to assemble such a series. So far as this study goes, then, it is not in disharmony with the conception of an acquired immunity to syphilis persisting in the absence of infection. On the other hand, it cannot be said to prove the correctness of that conception. The results of this study might also be taken to indicate that treatment fails to cure patients in the late stages of syphilis, or that persons who have once had syphilis and have been treated for it are not thereafter exposed to syphilitic infection to anything like the extent they formerly were. As to which explanation is correct, the future may decide.

SUMMARY AND CONCLUSIONS

1. A statistical study has been made of the cases reported in the literature since 1910 as examples of "reinfection," "superinfection" or second infection in syphilis.

2. Of the 676 cases reported, 447 have been considered to be unacceptable in accordance with the criteria outlined in the test. These unacceptable cases are listed with the references in the second part of the bibliography.

3. Two hundred and twenty-nine cases reported in the literature have been deemed acceptable, and to these have been added eight observed in the Syphilis Clinic of the Johns Hopkins Hospital, making a total of 237 patients.

4. Two hundred and thirty-two, or 97.8 per cent, of these patients were treated for the first infection during the primary or secondary stage.

5. Second infections occurred in four patients, or 1.6 per cent, who had had syphilis in a latent or late form (as evidenced by a positive Wassermann reaction without other signs indicating a primary or secondary stage) at the time they were first treated for the disease.

6. A second infection occurred in one patient, or 0.4 per cent, who presented undoubted evidence of congenital syphilis.

7. For the reasons previously discussed, second infections are expected to be, and are actually found to be, extremely rare in women.

8. There was not a single undoubted instance of a second infection in a patient who had, previously or concomitantly, had syphilis either of the central nervous system or of the heart and aorta.

9. The duration of the infection before the first treatment is known in 83 of the 232 patients who were first treated in the primary or secondary stage. It would indicate that virtually all were first treated before the end of sixteen weeks, and about 82 per cent before the end of eight weeks.

10. A close parallelism was observed, in man and in rabbits, between the relation of the time of treatment of the first infection and the incidence of second infections.

11. The relative frequency of a second attack of syphilis in patients who had been treated early for the first infection, as compared with the infrequency of second attacks in patients whose first infection had progressed to a latent or late stage before treatment indicates that the time of treatment for the first infection has an important bearing on the patient's acquired resistance to a second infection. It is pointed out that the relative infrequency of second infections in patients whose treatment had been begun late in the course of the disease is not in disharmony with the conception that acquired immunity to syphilis may persist in the absence of syphilitic infection.

REPORT OF CASES OF SECOND INFECTION WITH SYPHILIS AND ONE OF THIRD INFECTION

CASE 1.—*First Infection.*—A negro, born in 1892, had had lesions for several days when, on Dec. 19, 1921, an indurated ulcer appeared on the glans and several similar ulcers on the prepuce. Spirochetes were not demonstrated, and the Wassermann reaction was negative. During the next eight days, the patient received 49 cc. of tartar emetic, and the lesions healed rapidly.

On Jan. 13, 1922, after a genital lesion had been present for three days and a rash for two days, the patient had a sparse maculopapular syphilid; erosive lesions on the lips, papulo-erosive lesions on the uvula and serpiginous papulo-erosive lesions on the prepuce. From Jan. 13 to Dec. 22, 1922, the patient received irregular treatment, totaling fourteen injections of flumerin (which was being investigated clinically at this time) and five injections of arsphenamine; twenty Wassermann reactions were negative. On Dec. 7, 1922, the spinal fluid showed 7 cells; the globulin test was doubtful, and the mastic reaction was 4321000000.

On May 23, 1923, the patient returned after lesions had been present for three days. He had numerous papulo-erosive lesions on the glans, corona and shaft and a bilateral inguinal adenitis. Spirochetes were demonstrated. From May 23, 1923, to Jan. 29, 1924, the treatment was irregular, totaling eighteen injections of arsphenamine and mercurial inunctions and potassium iodide for six weeks. Fifteen Wassermann reactions were negative, as was the Wassermann test of the spinal fluid, on Nov. 11, 1924. On Dec. 5, 1924, physical examination revealed small, irregular, sluggish pupils, palpable epitrochlear glands and a sluggish right achilles' reflex.

Second Infection.—On Dec. 18, 1925, at another clinic, two penile "warts" were fulgurated; one disappeared, the other persisted. On December 28, the Wassermann reaction was positive. On Jan. 15, 1926, after the lesions had been present for four months, the patient had an elevated indurated lesion "as hard as cartilage" on the inner prepuce. Spirochetes were demonstrated. Treatment was given elsewhere.

CASE 2.—*First Infection.*—A white man, born in 1900, on Feb. 20, 1924, about twenty-eight days after exposure, noticed a painless genital lesion. A friend exposed to the same contact also acquired a genital lesion. On April 7, the Wassermann reaction was doubtful. On April 9, there was visible on the shaft of the penus a crusted ulcer with an indurated reddish base, and on the right side of the glans a superficial nonindurated lesion; there was also a bilateral inguinal adenitis. Spirochetes were not demonstrated, but serum from the lesion on the shaft gave a positive Wassermann reaction. From April 11 to August 6, the patient received twenty-six injections of arsphenamine and four courses of mercurial inunctions and potassium iodide, each course extending from four to sixteen weeks. To October 5, twenty-four Wassermann reactions were negative, as was the spinal fluid on June 13. Later the patient was in a sanatorium for six months because of a condition diagnosed as pulmonary tuberculosis.

Second Infection.—On December 17, after the lesions had been present for ten days, there appeared a small eroded indurated lesion in the coronal sulcus, without inguinal adenitis. Spirochetes were demonstrated; the Wassermann reaction was negative. The patient received treatment elsewhere.

CASE 3.—*First Infection.*—A white man, born in 1897, on Oct. 23, 1919, after lesions had been present for five days, presented three clean ulcers on the penis, a bilateral inguinal adenitis and a palpable left epitrochlear gland. Spirochetes were demonstrated. From October 24 to November 14, he received four injections of arsphenamine, and then left the clinic. Four Wassermann reactions were negative.

Second Infection.—On Jan. 21, 1921, after a lesion had been present for about two weeks, the patient had a round, indurated, ulcerated, "typical" lesion on the left side of the corona and a left inguinal adenitis. Spirochetes were demonstrated. On January 24, the Wassermann reaction was positive. From January 25 to March 1, the patient received six injections of arsphenamine; the first two Wassermann reactions were positive, the next three doubtful and the last negative. On March 10, the spinal fluid was normal. The patient did not return for further treatment.

CASE 4.—*First Infection.*—A white man, born in 1894, about Oct. 22, 1924, noticed several penile lesions, and several more appeared three days later. On November 2, he was supposed to have received an injection of arsphenamine from an outside physician. When he was in this clinic, on November 5, there were several shallow ulcers on the corona, one with a rolled edge and a parchment-

like base, and a bilateral inguinal adenitis. Spirochetes were demonstrated. From November 5 to December 11, the patient received irregular treatment, totaling eighteen injections of arsphenamine and twelve injections of bismuth. The first Wassermann reaction was suggestively positive, but sixteen subsequent tests were negative, as was the spinal fluid on September 26. The patient did not return to the clinic after December, 1925.

Second Infection.—On Sept. 1, 1926, after the lesion had been present for seven days, there was an indurated ulcer on the inner prepuce and a bilateral inguinal adenitis. Spirochetes were demonstrated. From September 1 to October 21, the patient received five injections of arsphenamine. Four Wassermann reactions were negative. He was then treated elsewhere.

CASE 5.—*First Infection.*—A white man, born in 1892, was first seen on Dec. 4, 1914. Six weeks before (about six weeks after exposure) there had been a penile lesion; three weeks before, an eruption developed on the back, face and knees; three days before, sores appeared in the mouth. Examination revealed a pharyngitis, a mucous patch on the left anterior pillar, a maculopapular eruption on the back, buttocks and extensor surfaces of the arms, an enlarged left epitrochlear gland, the remains of buboes and a scar on the inner prepuce. The patient received arsphenamine, 0.5 Gm., on December 4, 0.3 Gm. each on December 12 and 22, and 0.3 Gm. on Jan. 2, 1915; he did not return for further treatment. The Wassermann reaction was positive on December 4 and 13, negative on December 22, and doubtful on Jan. 2, 1915.

Second Infection.—The patient was next seen on Aug. 13, 1923. He had married in 1919, and his wife had had one healthy child and no miscarriages. For five days there had been a lesion, which had appeared about three weeks after exposure. Examination revealed on the mucous surface of the prepuce a clean, oval, indurated ulcer, covered with a yellowish-gray membrane; the base showed tiny red dots which represented thrombosed capillaries; there was also a general adenitis. Spirochetes were demonstrated, and the Wassermann reaction was positive. The patient received arsphenamine on the day of examination but did not return for further treatment.

Third Infection.—The patient was next seen on June 10, 1927. Since his last treatment, he had not received further therapy, and recently he had had many exposures. Five days before, a small lesion had appeared on the shaft. On the left side of the shaft in the mid portion, examination showed a round, indurated lesion, with a thin crust, exuding clear serum, in which spirochetes were demonstrated. There was a bilateral inguinal adenitis; the left epitrochlear was about the size of a small pea. Physical examination otherwise was negative. On the same day, the blood Wassermann reaction was negative, as was the spinal fluid (globulin test, 0; Wassermann reaction negative; mastic test, 0000000000).

CASE 6.—*First Infection.*—A white man, born in 1899, was exposed about May 12, 1922. On July 7, after lesions and enlarged glands had been present for six days, there appeared a round, painless, indurated ulcer on the inner prepuce, and a general adenitis was also present. Spirochetes were demonstrated. From July 7 to August 25, the patient received eight injections of arsphenamine; the second Wassermann reaction was suggestive positive, the other seven negative. The patient then did not come for further treatment until October 23, when the spinal fluid was negative. On November 4, the patient began a course of mercurial inunctions and potassium iodide.

Second Infection.—On Nov. 14, 1922, after a lesion had been present for about ten days, two recent and one indurated lesion were visibile in the sulcus. Spirochetes were demonstrated. On November 15, the Wassermann reaction was negative; on November 18, doubtful. From November 22 to December 27, the patient received six injections of arsphenamine. Four Wassermann reactions were positive and two negative. He then left the clinic.

CASE 7.—*First Infection.*—After a white man, born in 1894, had had gonorrhea and had received some intramuscular injections, he was seen elsewhere on April 30, 1919, with a general adenitis and a negative Wassermann reaction. On July 21, examination showed several penile lesions, which had been present for six weeks. Spirochetes were demonstrated, and the Wassermann reaction was positive. On July 28, there were scattered papules on the trunk, moist lesions on the glans and prepuce, a papulo-erosive lesion on the lip, general adenitis and alopecia. From July 28 to September 8, he received six injections of the meta-hydroxyanilid of arsenophenlyglycin (which was being investigated clinically at this time); five Wassermann reactions were positive and one doubtful. After receiving mercurial inunctions and potassium iodide for several weeks, the patient left the clinic. Three years later, on July 22 and Sept. 26, 1922, the Wassermann reaction was negative.

Second Infection.—On Jan. 16, 1923, there was a small penile lesion in which spirochetes could not be demonstrated; the Wassermann reaction was negative. On January 20, the lesion was indurated, but again spirochetes could not be demonstrated. On January 22, an indurated, painless, "typical" lesion on the prepuce, and bilateral inguinal adenitis were present. Spirochetes were demonstrated and the Wassermann reaction was negative. On January 24 and 31 and on February 7, the patient received injections of tryparsamide; then, because the lesion was increasing in size, the Wassermann reaction had become positive and spirochetes persisted, arsphenamine was administered, totaling eight injections to April 3. Of the eight Wassermann reactions during these injections, the first two were positive, the next two doubtful and the last four negative. After April 3, the treatment consisted of mercurial inunctions and potassium iodide for several weeks. On April 27, the spinal fluid was negative. The patient disappeared from the clinic without further treatment.

CASE 8.—*First Infection.*—A negro, born in 1891, had had headaches for three weeks, an eruption for one week, sore throat for three days and some loss of hair. On Aug. 31, 1921, an examination revealed an extensive eruption (macular, papular, pustular and follicular) in all stages, frambesiform lesions on the scalp, moist papules on the scrotum, urethritis, phimosis, an indurated nodule under the prepuce, an ulcerated syphilid on each tonsil and a general adenitis. From September 3 to October 26, he received eight injections of arsphenamine and then left the clinic. Of the Wassermann reactions, the first two were positive, the next doubtful and the remaining five negative. The patient returned to the clinic and received four injections of arsphenamine from Feb. 8 to March 28, 1922; the first Wassermann reaction was doubtful, the next positive, and the last two negative. He again discontinued treatment.

Second Infection.—On July 3, 1923, the Wassermann reaction was negative. On July 7, after a lesion had been present for about a week, the patient had a large, irregular ulcer involving the edge of, and extending under, the prepuce and on the glans. Spirochetes were demonstrated. On July 26, after an eruption had been present for three days, there was visible a large, flat, indurated pustular rash. Spirochetes were demonstrated in one of these lesions; on the same day, the spinal fluid was negative. From July 26, 1923, to Aug. 6, 1924,

the patient received nineteen injections of arsphenamine and had two courses of mercurial inunctions and potassium iodide, each course extending over six to eight weeks. Of the sixteen Wassermann reactions during this time, the first five were positive and the remaining eleven negative. The patient discontinued the clinic treatment.

BIBLIOGRAPHY

GENERAL

Antoni: Deutsche med. Wchnschr. **29**:508, 1913; cited by Benario.

Adachi: Acta derm.-venereol. **4**:393, 1925.

Arène: Bull. méd. **37**:152, 1923.

Arning: München. med. Wchnschr. **58**:922, 1911; cited by Benario.
Deutsche med. Wchnschr. **37**:1792, 1911.
} Same case report.

Arzt: Dermat. Wchnschr. **62**:337, 1921.

Audry: Ann. der dermat. et syph. **4**:160, 1913; cited by Benario.

Bais: Nederl. Tijdschr. v. Geneesk. **2**:1052, 1917.
Dermat. Wchnschr. **79**:978, 1924.

Balzer, Fouquet and Barthélemy: Bull. Soc. franç. de dermat. et syph. **25**: 242, 1914.

Benario: Die Reinfection bei Syphilis, Halle, Carl Marhold, 1914.

Berent: München. med. Wchnschr. **63**:1408, 1916.

Bering: München. med. Wchnschr. **58**:958, 1911.

Bernard and Tant: Réun. scient. de Bruxelles méd., Nov. 30, 1920; abstr., Ann. d. mal. vén. **17**:847, 1923.

Bettman: Dermat. Wchnschr. **54**:221, 1912; cited by Benario.

Biach, Wien. klin. Wchnschr. **26**:1363, 1913; cited by Benario.

Boas: München. med. Wchnschr. **60**:2620, 1913; cited by Benario.

Bogdanov: Acta derm.-venereol. **4**:115, 1923; abst., Zentralbl. f. Haut-u. Geschlechtskrankh. **10**:76, 1924.

Brenn: Mil. Surgeon **51**:250, 1922.

Brown and Pearce: J. Exper. Med. **33**:553, 1921.

Chargin: Syphilitic Reinfection, Arch. Dermat. & Syph. **1**:112 (Jan.) 1920.

Charmeil and Colpart: Echo méd. du nord. **16**:113, 1912.

Chesney: Medicine **5**:463, 1926.

Chesney and Kemp: J. Exper. Med. **39**:553, 1924.
J. Exper. Med. **42**:17, 1925.
J. Exper. Med. **44**:589, 1926.

Chesney, Halley and Kemp: J. Exper. Med. **46**:223, 1927.

Clement: Bull. Soc. franç. de dermat. et syph. **28**:106, 1921.

Cornaz: Rev. méd. de la Suisse Rom. **42**:453, 1922.

Dössekker: Schweiz. med. Wchnschr. **2**:137, 1921.

Driver: Reinfection in Syphilis, J. A. M. A. **83**:1728 (Nov. 29) 1924.

Duhot: Ann. de la policlin. centr. de Bruxelles. (Okt.), no. 10, 1911; cited by Benario.
Rev. belge. d'urol., no. 7, 1912; cited by Benario.

Fernet: Bull. Soc. franç. de dermat. et syph. **25**:358, 1914.

Finger: Arch. f. Dermat. u. Syph. **129**:344, 1921.

Fischel: Dermat. Ztschr. **34**:332, 1921.

Frei: Arch. f. Dermat. u. Syph. **144**:365, 1923.

Frey: Schweiz. med. Wchnschr. **1**:1183, 1920.

Frühwald: Arch. f. Dermat. u. Syph. **123**:318, 1916. } Same case report
Wien. klin. Wchnschr. **30**:1161, 1917. } (one case)

Gager: Urol. & Cutan. Rev. **27**:13, 1923.
Gaston and Sanglier-Lamark: Bull. Soc. franç. de dermat. et syph. **23**:468, 1912; cited by Benario.
Gennerich: München. med. Wchnschr. **60**:2460, 1913; cited by Benario.
Gennerich and Zimmern: Dermat. Ztschr. **26**:133, 1918.
Geyer: Deutsche med. Wchnschr. **37**:1522, 1911; cited by Benario.
Gibbard, Harrison and Cane: J. Roy. Army Med. Corps **19**:291, 1912; cited by Benario.
Goldenberg and Chargin: J. Cutan. Dis. **37**:215, 1919. } Same case
J. Cutan. Dis. **37**:333, 1919. } report.
Gougerot and Fernet: Bull. Soc. franç. de dermat. et syph. **30**:247, 1923.
Gutmann: Berl. klin. Wchnschr. **48**:1282, 1911; cited by Benario.

Hanacek: Dermat. Wchnschr. **54**:188, 1912; cited by Benario.
Hecht: Arch. f. Dermat. u. Syph. **124**:327, 1919.
Dermat. Wchnschr. **72**:97, 1921; **77**:1053, 1923.
Zentralbl. f. Haut-u. Geschlechtskr. **9**:85, 1924.
Deutsche med. Wchnschr. **38**:703, 1912; cited by Benario.
Hell: Arch. f. Dermat. u. Syph. **124**:443, 1917.
Hoffmann: Fortschr. d. Erk. u. Behandl. d. Syph., Bonn, 1913; cited by Benario. } Same case report.
München. med. Wchnschr. **61**:2063, 1914. }
Hutchinson: Arch. Surg., London **4**:113, 1895.
Proc. Roy. Soc. Med. **2**:225, 1908-1909.

Isacson: Med. Klin. **17**:533, 1921.

Jeanselme and Althabégoity: Bull. Soc. franç. de dermat. et syph. **28**:10, 1921.
Jeanselme and Burnier: Bull. Soc. franç. de dermat et syph. **28**:401, 1921.
Jeanselme and Vernes: Bull. Soc. franç. de dermat. et syph. **22**:353, 1911; cited by Benario.
Jenssen, quoted by Benario.
Jersild: Dermat. Ztschr. **28**:43, 1919.
Jullien: Bull. méd., July 7, 1912; cited by Benario.

Kilroy: Lancet. **1**:302, 1913.
Klauder: J. Cutan. Dis. **39**:515, 1918.
Klausner: Dermat. Wchnschr. **65**:951, 1917.
Kolle: Deutsche med. Wchnschr. **48**:1301, 1922.
Deutsche med. Wchnschr. **50**:17, 1924.
Krefting: Paris méd. **9**:245, 1913.
Deutsche med. Wchnschr. **37**:1441, 1911; cited by Benario.

Lagage: Ann. d mal. vén. **14**:685, 1921.
Laurent: Bull. Soc. franç. de dermat. et syph. **27**:15, 1920 } Same case report
Loire Méd. **34**:67, 1920. } (one case).
Lépinay: Bull. Soc. franç. de dermat. et syph. **29**:124, 1922.
Lesser: Deutsche med. Wchnschr. **67**:1425, 1921.
München. med. Wchnschr. **61**:542, 1914; cited by Benario.
Levin: Med. Klin. **13**:736, 1917.
Superinfection; Syphilis. Arch. Dermat. & Syph. **6**:231 (Aug.) 1922.
Lévy-Franckel and Sauget: Ann. d mal. vén. **16**:248, 1921.
Lohe: Berl. klin. Wchnschr. **50**:922, 1913; cited by Benario.

Mariani: Policlinico **20**:337 (Aug.) 1913; cited by Benario.
Melun: Ann. d. mal. vén. **7**:128, 1912; cited by Benario.
Meschtschersky: Wratschebnoje Djebo, vol. 304, 1922; abstr., Zentralbl. f. Haut-u. Geschlechtskr. **7**:399, 1923.
Milian: Bull. et mém. Soc. méd. d. hôp. de Paris **30**: 715, 1910; cited by Benario.
Bull. Soc. franç. de dermat. et syph. **22**:202, 1911. } Same case report. (one case)
Minassian: Gior. ital. d. mal. vén. **63**:809, 1922; abstr. Ann. d. mal. vén. **18**: 63, 1923.
Moldovan: München. med. Wchnschr. **59**:1902, 1912; cited by Benario.
Mouradian: Ann. d. mal. vén. **17**:838, 1922.
Müller: Arch. f. Dermat. u. Syph. **123**:593, 1916.
Mullern-Aspegren: Dermat. Ztschr. **20**:1078, 1913; cited by Benario.
Neisser: Arb. a. d. k. Gsndhtsamte. **37**:1, 1911.
Nelson: Ohio State M. J. **15**:726, 1919.
Eclectic M. J. **80**:170, 1920.
Eclectic M. J. **80**:536, 1920. } Same case report.
Odstrcil: Dermat. Wchnschr. **65**:654, 1917.
Oltramare: Ann. d mal. vén. **16**:661, 1921.
Oppenheim: Wien. klin. Wchnschr. **23**:1774, 1910; cited by Benario.
Parounagian: Reinfection in Syphilis, Arch. Dermat. & Syph. **7**:126 (Jan.) 1923.
Syphilitic Reinfection, ibid. **12**:279 (Aug.) 1925.
Syphilitic Reinfection, ibid. **12**:125 (Aug.) 1925.
Reinfection in Syphilis, ibid. **11**:865 (June) 1925. } Same case report (one case).
Pinard and Deguignaud: Bull. et mém. Soc. méd. d. hôp. de Paris **45**:1415, 1921.
Pollitzer: General Prognosis of Syphilis in Light of Recent Progress, J. A. M. A. **74**:775 (March 20) 1920.
Pontoppidan: Dermat. Wchnschr. **64**:540, 1917.
Queyrat: Bull. et mém. Soc. méd. d. hôp. de Paris **36**:291, 1913; cited by Benario.
Reasoner: Am. J. Syph. **8**:313, 1924.
Reiter: Klin. Wchnschr. **5**:1356, 1926.
Riecke: München. med. Wchnschr. **60**:2703, 1913; cited by Benario.
Ricord, quoted by Hutchinson.
Schleicher: Dermat. Ztschr. **21**:397, 1914.
Schoenrich: Am. J. Syph. **7**:53, 1923.
Schueller: Berl. klin. Wchnschr. **49**:155, 1912; cited by Benario.
Sweitzer: Reinfection in Syphilis, J. A. M. A. **66**:1196 (April 15) 1916.
Seraphi: Ann. d. mal. vén. **15**:439, 1920.
Spitzer: Wien. klin. Wchnschr. **26**:1396, 1913; cited by Benario.
Steinmetz: Rev. méd. de la Suisse Rom. **41**:335, 1921; case cited also by Oltramare.
Stokes: Modern Clinical Syphilology, Philadelphia, W. B. Saunders Company, 1926.
Stühmer: München. med. Wchnschr. **58**:893, 1911; cited by Benario.
Stümpke: Deutsche med. Wchnschr. **38**:1041, 1912; cited by Benario.
Tashiro: Acta derm.-venerol. **8**:753, 1926.
Thibierge: Bull. méd. **34**:953, 1920.

Thompson: A Case of Possible Third Infection with Syphilis, J. A. M. A. **81**:2114 (Dec. 22) 1923.

Troude: Ann. d. mal. vén. **18**:850, 1925.

Western: Brit. J. Dermat. **26**:280, 1914.

White: Brit. M. J. **2**:509, 1917.

Whiteside: Ann. d mal. vén. **6**:682, 1911; cited by Benario.

Williams: Syphilitic Reinfection, Arch. Dermat. & Syph. **1**: 702 (June) 1920.
Secondary Syphilitic Infection, Arch. Dermat. & Syph. **30**: 126 (Feb.) 1921.
} Same case report.

Wirz: München. med. Wchnschr. **70**:429, 1923.

Wüstenberg: München. med. Wchnschr. **59**:1666, 1912; cited by Benario.

Zeissel: Wien. klin. Wchnschr. **24**:596, 1921.

Zimmern: Deutsche med. Wchnschr. **38**:1691, 1912; cited by Benario.

UNACCEPTABLE CASES

Abulov: Russ. Ztschr. f. Haut-u. venerische Krnkhtn., Jan., 1910, vol. 19; abstr., Monatsch. f. prakt. Dermat. **50**:358, 1910 (one case).

Aemkvist: Acta derm.-venerol. **1**:459, 1921; abstr., Zentralbl. f. Haut-u. Geschlechtskrankh. **3**:480, 1922 (two cases).

Armstrong: Syphilitic Reinfection, Arch. Dermat. & Syph. **3**:476 (April) 1921 (one case).

Arning: Deutsche med. Wchnschr. **44**:647, 1918 (one case).

Arzt: Zentralbl. f. Haut-u. Geschlechtskrankh. **1**:20, 1921 (one case).
Zentralbl. f. Haut-u. Geschlechtskrankh. **1**:218, 1921 (one case).
Zentralbl. f. Haut-u. Geschlechtskrankh. **3**:430, 1922 (one case).
Zentralbl. f. Haut-u. Geschlechtskrankh. **4**:98, 1922 (one case).
Zentralbl. f. Haut-u. Geschlechtskrankh. **6**:504, 1923 (one case).

Bais: Nederl. Tijdschr. v. Geneesk. **2**:1052, 1917.
Dermat. Wchnschr. **79**:978, 1924.

Ballenger and Elder: M. Rec. **80**:1126, 1911 (one case).

Baum: Zentralbl. f. Haut-u. Geschlechtskrankh. **9**:389, 1924 (one case).

Belgodère: Ann. d. mal. vén. **16**:693, 1921 (one case).
Ann. d. mal. vén. **17**:823, 1922 (one case).

Bélin, Milian and Amaudraut: Bull. et mém. Soc. méd. d. hóp. de Paris **33**: 224, 1912; cited by Benario (one case).

Bethune: Buffalo M. J. **72**:113, 1916 (one case).

Bechet: J. Cutan. Dis. **37**:475, 1919 (one case).

Blackshear: J. M. A. Georgia **5**:129, 1915-1916 (one case).

Boas: Dermat. Ztschr. **22**:79, 1915 (one case).
Ugesk. f. Laeger. **77**:1579, 1916; abstr., Dermat. Wchnschr. **64**:310, 1917 (one case).
Dermat. Ztschr. **28**:40, 1919 (one case).

Bogdanov: Acta derm.-venerol. **4**:115, 1923 (two cases).

Bonnet: Lyon med. **12**:600, 1909 (one case).

Brandt: Wien. med. Wchnschr. **70**:278, 1920 (one case).

Brandweiner: Wien. klin. Wchnschr. **30**:1483, 1917 (one case).

Breide: Acta derm.-venereol., 1920; abstr., Dermat. Wchnschr. **73**:1093, 1921 (one case).
Ibid. **1**:456, 1921; abstr., Zentralbl. f. Haut-u. Geschlechtskrankh. **4**:58, 1922 (one case).

Brew: M. Rec. **72**:138, 1907 (one case).

Broc and Fernet: Bull. Soc. franç. de dermat. et syph. **22**:343, 1911; cited by Benario, but not cited by authors as "reinfections" (two cases).

Bruck: München. med. Wchnschr. **69**:1624, 1922 (three cases).

Brun-Pederson: Hospitalstid. **64**:73, 1921; abstr. Zentralbl. f. Haut-u. Geschlechtskrankh. **3**:238, 1922 (one case).

Burgsdorf: Russk. Vrach. **7**:146, 1908; trans. Klin.-therap. Wchnschr. **15**: 594, 1908 (one case).

Carle: Ann. d. mal. vén. **16**:345, 1921 (one case).
Ann. d. mal. vén. **17**:487, 1922 (one case).
Ann. d. mal. vén. **17**:629, 1922 (one case).

Cassar: Ann. de dermat. et syph. **6**:376, 1916-1917 (one case).

Chargin: Syphilitic Reinfection, Arch. Dermat. & Syph. **7**:256 (Jan.) 1923 (one case).

Conrad: A Case of Possible Superinfection, Arch. Dermat. & Syph. **7**:866 (June) 1923 (one case).

Corbus: New York M. J. **100**:472, 1914 (one case).

Cornaz: Rev. méd. de la Suisse Rom. **42**:453, 1922.

Covisa and Nonell: Acta dermo.-sifil. Oct.-Nov., 1911, vol. 4; abstr. Dermat. Wchnschr. **55**:862, 1912. } Same case reports (one case).

Covisa and Nonell: Rev. clin. de Madrid **8**:65, 1912; abstr. Dermat. Wchnschr. **55**:1563, 1912. } Same case reports (one case).

Cunningham: Boston. M. & S. J. **166**:929, 1912; cited by Benario.
M. & Surg. Rep. City Hosp. **16**:112, 1913. } Same case reports (two cases).

Da Silva: Bull. Soc. franç. de dermat. et syph. **23**:178, 1912; cited by Benario (one case).

De la Portilla: Acta dermo.-sifil., Dec., 1919, Jan., 1920, no. 2; abstr., Dermat. Wchnschr. **72**:384, 1921 (one case).
Acta dermo.-sifil., April-May, 1921, p. 147; abstr., Ann. d. mal. vén. **27**:527 (two cases).
Acta dermo.-sifil. **13**:77, 1921; abstr., Zentralbl. f. Haut-u. Geschlechtskrankh. **3**:380, 1922 (one case).
Acta dermo-sifil. **14**:232, 1922; abstr., Zentralbl. f. Haut-u. Geschlechtskrankh. **6**:107, 1923 (one case).

De Lyon: Ann. d. mal. vén. 1921; cited by Louis Rene (one case).

Dardenne: Lancet **2**:1071, 1909 (one case).

Deioide: Bull. et mém. Soc. méd. d. hôp. de Paris **41**:603, 1917 (one case).

Dohi, Watanabe and Nokogima: Japan. Ztschr. f. Dermat., June, July, 1912; abstr. Dermat. Ztschr. **21**:459, 1913; cited by Benario (one case).

Doucy and Joltrain: J. de med. int. **15**:220, 1911 (one case).

Driver: Reinfection in Syphilis, J. A. M. A. **83**:1728 (Nov. 29) 1924.

Dupuylatat de Laviergne: Thèse de Paris, 1913; cited by Benario.
Gaz. d. prat. **21**:83, 1914. } Same case report (one case).

Fabry: Med. Klin. **9**:2112, 1913; cited by Benario (one case).
Med. Klin. **7**:1201, 1911 (one case).

Fabry and Jerzycki: Med. Klin. **8**:189, 1912; cited by Benario (two cases).

Finger: Arch. f. Dermat. u. Syph. **129**:344, 1921 (one case).

Fiocco: Gior. ital. di dermat. e sifil. **66**:1287, 1925; abstr., Zentralbl. f. Haut-u. Geschlechtskrankh. **18**:803, 1926 (one case).

Fischel: Zentralbl. f. Haut-u. Geschlechskrankh. **1**:105, 1921 (one case).
Zentralbl. f. Haut-u. Geschlechtskrankh. **16**:883, 1925 (one case).
Fitzgibbon: Dublin J. M. Sc. **130**:337, 1910 (one case).
Flaudin, in discussion on Lacapére (one case).
Fonss: Hospitalstid. **64**:22, 1921; abstr. Zentralbl. f. Haut-u. Geschlechtskrankh. **3**:237, 1922 (one case.)
Forns: Acta dermo.-sifil., Oct.-Nov. 1914, no. 1, p. 51; Ann. d. mal. vén. **12**: 231, 1917 (one case).
Fournier: Rev. prat. des mal. des organes genito-urinaires, **9**:313, 1912; abstr., Dermat. Wchnschr. **55**:1335, 1912 (one case).
Freund: München. med. Wchnschr. **63**:64, 1916 (three cases).
Friedländer: Berl. klin. Wchnschr. **58**:321, 1921 (two cases).
Frühwald: Arch. f. Dermat. u. Syph. **123**:318, 1916; Wien. klin. Wchnschr. **30**:1161, 1917 (one case).
Galliot: Paris méd. **43**:194, 1922 (one case).
Gastinel: Ann. d. mal. vén. **10**:641, 1914 (one case).
Gaston: Bull. Soc. franç. de dermat. et syph. **23**:471, 1912 (one case).
Gaucher, Gougerot and Guggenheim: Bull. Soc. franç. de dermat. et syph. **22**:149, 1911 (two cases).
Gennerich: Ztschr. f. Chemotherap. **1**:69, 1912 (one case).
München. med. Wchnschr. **60**:2460, 1913; cited by Benario (four cases).
München. med. Wchnschr. **61**:513, 1914 (no case report).
Gennerich and Zimmern: Dermat. Ztschr. **26**:133, 1918 (eight cases).
Geyer: Deutsche. med. Wchnschr. **37**:1522, 1911; cited by Benario (two cases).
Gibbard, Harrison and Cane: J. Roy. Army Med. Corps **19**:291, 1912; cited by Benario (one case).
Gittings: Brit. M. J. **1**:891, 1912 (one case).
Glavtché: Ann. d. mal. vén. **8**:666, 1913; cited by Benario (two cases).
Glowsche: Dermatologia (russich) **1**:697, 1913; abstr., Dermat. Ztschr, **21**: 461, 1914 (two cases).
Goizet: Ann. d. mal. vén. **6**:254, 1911 (one case).
Goubeau: Presse méd. **25**:325, 1917 (one case).
Graham: Edinburgh M. J. **8**:442, 1912; cited by Benario (one case).
Guiard: Progres méd., 1911, p. 245.
Ann. d. mal. vén. **6**:81, 1911.
J. des practiciens **29**:150, 164 and 181, 1915.
} Same case report (one case).
Hallopeau: Arch. f. Dermat. u. Syph. **106**:231, 1911 (one case).
Ann. d. mal. vén. **7**:362, 1912 (two cases).
Arch. f. Dermat. u. Syph. **113**:397, 1912 (one case).
Hanacek: Dermat. Wchnschr. **54**:188, 1912; cited by Benario (one case).
Hardrat: München. med. Wchnschr. **61**:541, 1914; cited by Benario (two cases).
Hecht: Arch. f. Dermat. u. Syph. **124**:327, 1919 (case reports no. 28 and 32) (two cases).
Heiner: Orvosi hetil. **68**:129, 1924; abstr., Zentralbl. f. Haut-u. Geschlechtskrankh. **13**:294, 1924 (one case).
Henningsen: Dermat. Ztschr. **28**:40, 1919 (one case).
Hesse: Dermat. Centralbl. **13**:355, 1910 (one case).
Hofmann and Mergelsberg: Dermat. Ztschr. **35**:1, 1922 (twelve cases).
Hudelo and Jolivet: Bull. Soc. franç. de dermat. et syph. **22**:430, 1911 (one case).

Ingram: Brit. M. J. **1**:1291, 1923 (three cases).
Irvine: Brit. M. J. **1**:765, 1917 (one case).
Iwanov: Dermatologia (russisch.) **2**:1242, 1913; abstr., Dermat. Ztschr. **21**: 1018, 1914 (one case).
Referred to by Wirz (one case).

Jaegnet: Bull. et mém. Soc. méd. d. hôp. de Paris **29**:750, 1910 (three cases).
Jeanselme: J. de méd. de Paris **28**:33, 1919 (one case).
Jeanselme and Vernes: Bull. Soc. franç. de dermat. et syph. **22**:353, 1911; cited by Benario (one case).
Jersild: Hospitalstid. **64**:33, 1921; abstr., Zentralbl. f. Haut-u. Geschlechtskrankh. **3**:380, 1922 (one case).
Jordan: Dermat. Wchnschr. **76**:453, 1923 (two cases).
Jörgensen: Norsk. Mag. f. Laegevidensk. **11**:786, 1913; abstr., Deutsche med. Wchnschr. **39**:1331, 1913; cited by Benario (one case).

Kermorgant: Bull. et mém. Soc. méd. d. hôp. de Paris **41**:886, 1917 (one case).
Klauder: J. Cutan. Dis. **6**:515, 1918 (three cases).
Klotz: Tr. Am. Dermat. A. **28**:83, 1904 (one case).
Kransz, cited by Benario (one case).
Krefting: Norsk. Mag. f. Laegervidensk. **13**:1223, 1915; abstr., Dermat. Wchnschr. **64**:310, 1917 (one case).
Krösl: Dermat. Wchnschr. **80**:873, 1925; abstr., Zentralbl. f. Haut-u. Geschlechtskrankh. **18**:600, 1926 (one case).
Kyrle: Wien. klin. Wchnschr. **37**:1105, 1924 (one case).

Lacapère: Bull. Soc. franç. de dermat. et syph. **23**:466, 1912; cited by Benario (one case).
Bull. Soc. franç. de dermat. de syph. **29**:120, 1922 (one case).
Lacapère and Galliot: Bull. Soc. franç. de dermat. et syph. **26**:238, 1919 (one case).
Lambrior: Bull. Soc. des méd. et naturalistes de Jassy **20**:201, 1906; abstr., Ann. d. vén. **2**:132, 1907 (three cases).
Laviergne: Am. J. Urol. and Sexol. **12**:10, 1916 (one case).
Lessen: Deutsche med. Wchnschr. **67**:1425, 1921 (four cases).
Lesczynski: Zentralbl. f. Haut-u. Geschlechtskrankh. **15**:149, 1925 (one case).
Lichtenstein: Wien. klin. Wchnschr. **29**:1208, 1916 (one case).
Lier: Wien. klin. Wchnschr. **27**:867, 1914 (one case).
Lipschutz: Arch. f. Dermat. u. Syph. **109**:3, 1911 (two cases).
Lipskerow: Venerologija i Dermatologija, 1924, p. 13; abstr., Zentralbl. f. Haut-u. Geschlechtskrankh. **18**:90, 1926 (one case).
Lipskeroff and Minsker: Venerologija i Dermatologija, 1925, 34; abstr., Zentralbl. f. Haut-u. Geschlechtskrankh. **17**:671, 1925 (one case).

McDonagh: Brit. J. Dermat. **23**:227, 1911 (one case).
Makris: Grèce méd. **26**:39, 1924; abstr., Zentralbl. f. Haut-u. Geschlechtskrankh. **14**:234, 1924 (one case).
Malherbe: Gaz. med. de Nantes **31**:201, 1913 (one case).
Manuel: Proc. Roy. Soc. Med. **4**:30, 1910-1911 (one case).
Mariotti: Gior. ital. d. mal. ven. **51**:185, 1916; abstr., Dermat. Wchnschr. **64**:71, 1917 (two cases).
Massion and Hervier: Bull. Soc. med. clin. de L'Indo-Chine **4**:159, 1913; cited by Benario (one case).
Merck, cited by Benario (one case).

Milian: Bull. Soc. franç. de dermat. et syph. **21**:83, 1910 (one case).
Bull. Soc. franç. de dermat. et syph. **22**:350, 1911; cited by Benario (three cases).
Milian and Sauphar: Bull. Soc. franç. de dermat. et syph. **24**:7, 1913; cited by Benario (one case).
Moldovan: München. med. Wchnschr. **59**:1902, 1912; cited by Benario (one case).
Morath: München. med. Wchnschr. **69**:1575, 1922 (one case).
Morelle: Ann. de L'Inst. chir. de Bruxelles **18**:65, 1911.
Presse méd. belge **63**:326, 1911.
J. méd. de Bruxelles **16**:56, 1911; abstr., Dermat. Centralbl. **14**:319, 1911.
} Same case report (one case).
Mouradian: Ann. d. mal. vén. **17**:838, 1922 (three cases).
Mrougowius: Russk. Vrach., 1912, no. 26; abstr., Dermat. Wchnschr. **55**:1563, 1912; cited by Benario (one case).
Müller: Arch. f. Dermat. u. Syph. **123**:393, 1916 (sixteen cases).
Müllern-Aspergren: Dermat. Ztschr. **20**:1078, 1915; cited by Benario (one case).
Murero: xvii riun. d. soc. ital. di derm. e sifil., June, 1920; abstr., Zentralbl. f. Haut-u. Geschlechtskrankh. **5**:317, 1922 (three cases).
Mutschler: Arch. f. Dermat. u. Syph. **147**:107, 1924 (two cases).
Nelken: Lancet-Clinic. **114**:233, 1915 (three causes).
Nichols: The Present Status of Salvarsan Therapy in Syphilis, J. A. M. A. **58**:603 (March 2) 1912 (one case).
A Second Initial Lesion of Syphilis One Year After the First, J. A. M. A. **80**:843 (March 24) 1923 (one case).
Nikolski: Zentralbl. f. Haut-u. Geschlechtskrankh. **9**:334, 1924 (two cases).
Odstcil: Dermat. Wchnschr. **65**:654, 1917 (two cases).
Oltramare: J. d. mal. Cutat. et de Syph. **17**:92, 1905 (one case).
Ann. d. mal. vén. **16**:661, 1921 (seven cases).
Oplatek: Wien. klin. Wchnschr. **20**:441, 1907, bibliography (one case).
Oppenheim: Zentralbl. f. Haut-u. Geschlechtskrankh. **1**:108, 1921 (one case).
Oro: Rif. med. **41**:268, 1925; abstr., Zentralbl. f. Haut-u. Geschlechtskrankh. **17**:671, 1925 (one case).
Orphanides: Ann. d. mal. vén. **17**:217, 1922 (one case).
Papée: Zentralbl. f. Haut-u. Geschlechtskrankh. **16**:522, 1925 (one case).
Pappagallo: Gior. ital. d. mal. vén. **54**:302, 1913; cited by Benario (one case).
Parounagian: New York M. J. **103**:153, 1916 (one case).
Syphilitic Reinfection, Arch. Dermat. & Syph. **8**:98 (July) 1923 (one case).
Parounagian and Mason: Reinfection in Syphilis, Arch. Dermat. & Syph. **11**:865 (May) (one case).
Pártos: Wien. klin. Wchnschr. **31**: 640, 1918 (one case).
Pawlow: Russky Wiestnick Dermatologii. 19, 1924; abstr., Zentralbl. f. Haut-u. Geschlechtskrankh. **16**:915, 1925 (one case).
Payenneville: Normandie méd. **31**:133, 1921 (one case).
Peyri: Acta dermo.-sifil., Feb.-March, 1917, p. 119; abstr., Ann. d. mal. vén. **13**:315, 1918 (one case).
Piccardi: Gior. ital. d. mal. ven e d. pelle **63**:477, 1922; abstr., Zentralbl. f. Haut-u. Geschlechtskrankh. **6**:184, 1923 (twelve cases).
Pinard: Bull. Soc. franç. de dermat. et syph. **26**:228, 1919 (one case).
Ann. d. mal. vén. **15**:722, 1920 (one case).

Pöhlman: München. med. Wchnschr. **61**:2200, 1914 (one case).
Polland: Wien. klin. Wchnschr. **21**:1705, 1908 (one case).
Wien. klin. Wchnschr. **37**:162, 1924 (two cases).
Pontoppidan: Arch. f. Dermat. u. Syph. **136**:135, 1921 (thirty-seven cases).
Posdujakow: Klin. med., 1922, vol. 37; abstr., Zentralbl. f. Haut-u. Geschlechtskrankh. **7**:104, 1923 (one case).
Queyrat: Bull. et mém. Soc. méd. d. hôp de Paris **32**:720, 1911 (one case).
Demanche and Pinard: Bull. et mém. Soc. méd. d. hôp. de Paris **37**:379, 1914; cited by Benario (one case).
Rathner: Russki Wiestnick Dermatologii **3**:149, 1925; abstr., Zentralbl. f. Haut-u. Geschlechtskrankh. **17**:464, 1925 (one case).
Reasoner: Am. J. Syph. **8**:313, 1924 (four cases).
Renault: Bull. et mem. Soc. méd. d. hôp. de Paris **29**:1097, 1915 (one case).
J. des. practiciens **29**:783, 1915. } Same case report
In discussion of Jeanselme and Althabégoity. } (one case).
René (Louis): La réinfection syphylitique, thèse, 1923 (one case).
Richards: U. S. Nav. M. Bull. **9**:651, 1915 (one case).
Ries and Leypen: Med. Corres.-Bl. des württemb. Landesvereins **82**:510, 1912 (two cases).
Roederer and Camus: Bull. Soc. franç. de dermat. et syph. **28**:62, 1921 (one case).
Sains de Azua, cited by Peyri (one case).
Acta dermo.-sifil., Oct.-Nov., 1917, vol. 39; abstr., Ann. d. mal. vén. **14**: 565, 1919 (two cases).
Salmon: Bull. Soc. de L'Internat. 1912, no. 2; cited by Benario (one case).
Sanz de Grado: Acta. dermo.-sifil., Dec.-Jan., 1919-1920, no. 2; abstr., Dermat. Wchnschr. **72**:385, 1921 (one case).
Saphier: Wien. klin. Wchnschr. **27**:1058, 1914 (one case).
Sarrat: Ann. d. mal. vén. **16**:700, 1921 (one case).
Schamberg: Second Attack of Syphilis Two Years After First, J. A. M. A. **73**:826 (Sept. 13) 1919 (one case).
Progressive Med. **3**:228, 1922 (one case).
Progressive Med., Sept., 1922, p. 251 (one case).
Scholtz: Deutsche med. Wchnschr. **38**:309, 1912; cited by Benario (one case).
Scott: Brit. M. J. **2**:1344, 1913 (five cases).
Seeliger: Soc. méd. chir. de Liège, Dec. 7, 1911; cited by Benario (one case).
Selenef: Russische Ztschr. f. Haut-u. Geschlechtskrankh. **7**:10, 1907; abstr., Dermat. Centralbl. **13**:160, 1910 (four cases).
Selenew: Dermat. Centralbl. **14**:98, 1910-1911.
Russische Ztschr. f. Haut-u. ven. Krankh. Jan., 1910, vol. 19; abstr., Monatschr. f. prak. Dermat. **50**:358, 1910. } Same case report (two cases).
Shaw: Brit. M. J. **1**:777, 1912; cited by Benario (one case).
Silberstein: Arch. f. dermat. u. syph. **143**:334, 1923 (seven cases).
Sirota: Deutsche med. Wchnschr. **50**:1585, 1924 (one case).
Smith: M. Rec. **88**:60, 1915. } Same case report
New York M. J. **102**:374, 1915. } (one case).
Spangenthal: Syphilitic Reinfection, J. A. M. A. **71**:730 (Aug. 31) 1918 (one case).
Spence: Proc. Roy. Soc. Med. **9**:96, 1915 (one case).
Ssachnowskaja and Schestakowa: Venereologija i Dermatologija, 27, 1925; abstr., Zentralbl. f. Haut-u. Geschelechtskrankh. **18**:90, 1926 (two cases.

Stein: Klin. med. (russisch), 1922, vol. 14; abstr., Zentralbl. f. Haut-u. Geschlechtskrankh. **7**:103, 1923 (three cases).

Stern: Dermat. Ztschr. **14**:197, 1907. } Same case report
Deutsche med. Wchnschr. **33**:123, 1907. } (one case).
Deutsche med. Wchnschr. **29**:1247, 1913 (one case).

Stokes, O'Leary and Goeckerman: Arch. Dermat. & Syph. **4**:849, 1921 (one case).

Stümpke: Zentralbl. f. Haut-u. Geschlechtskrankh. **5**:441, 1922 (one case).

Suggett: New York M. J. **91**:790, 1910 (two cases).

Swerew: Russk. Vrach., 1911, p. 1473; abstr., Dermat. Ztschr. **19**:370, 1912 (one case).

Swinburne: J. Cutan. Dis. **25**:468, 1907. } Same case report
Tr. 6th Int. Dermat. Cong. **2**:825, 1907. } (one case).

Tartaru: Ann. de dermat. et syph. **4**:243, 1923 (two cases).

Tièche: Dermat. Wchnschr. **61**:46, 1916; abstr., Dermat. Ztschr. **23**:564, 1916 (two cases).

Tommasi: Gior. ital. d. mal. ven. e. d. pelle **63**:473, 1922; abstr., Zentralbl. f. Haut-u. Geschlechtskrankh. **6**:184, 1923 (one case).

Triaud: De la réinfection syphilitique, Thèse, 1919 (three cases).

Ullmann: Dermat. Ztschr. **18**:1065, 1911; cited by Benario (one case).

Valverde: Brazil-med. **2**:279, 1924; abstr., Zentralbl. f. Haut-u. Geschlechtskrankh. **18**:803, 1926 (one case).

Van Gant: Dermatologia (russisch) **2**:1410, 1913; abstr., Dermat. Ztschr. **21**:1018, 1914 (one case).

Vanhaecke: Echo méd. du nord. **17**:251, 1913 (one case).

Van Rhee: Syphilitic Reinfection, Arch. Dermat. & Syph. **10**:240 (July) 1924 (one case).

Vilanova: Acta derma.-sifil., Feb.-March, 1918, p. 139; abstr., Ann. d. mal. vén. **14**:383, 1919 (one case).

Westcope: Brit. M. J. **2**:109, 1916 (two cases).

White: Brit. M. J. **2**:509, 1917 (twenty-two cases).

Williams: Lancet-Clinic **100**:178, 1908. Same case report.
M. Fortnightly **32**:485, 1907. } (one case).

Wood: New York M. J. **94**:26, 1912; cited by Benario (same as Whiteside).

Yerouchalmi: Ann. d. mal. vén. **16**:690, 1921 (one case).

Zak: J. russe d. mal. cutat. et vénér., March, 1914, p. 201; abstr., Ann. d. mal. vén. **10**:307, 1915 (two cases).

Zaun: St. Paul M. J. **14**:115, 1912 (one case).

Zieler: München. med. Wchnschr. **67**:886, 1920 (one case).

PANCREATIC FUNCTION AND UPPER INTESTINAL DIGESTION

A NEW METHOD OF STUDY *

SANFORD M. ROSENTHAL, M.D.
MONTREAL

The methods at present available for determining the activity of the external pancreatic secretion are based chiefly on the estimation of the enzyme concentration of the duodenal contents and the presence of fat and starches in the stools. Such methods are helpful in advanced disease, but wide normal variations detract from their usefulness in earlier diagnosis and discourage their employment in laboratory experimentation.

The method which I have evolved is based on the estimation of the digestion of starch in the upper intestine. This is accomplished by giving starch by mouth, and studying the rate at which it is broken down by following the rise in blood sugar.

Traces of diastatic ferments are present in most body fluids, but they are produced in quantity only by the salivary glands and pancreas. Hahn and Meyer [1] found that the amylase from these two sources has similar enzymatic properties. Its activity is dependent on the hydrogen ion concentration of the medium. Willstatter [2] found the activity greatest at p_H 6.8, and Sherman [3] has shown that it is entirely inhibited at p_H 4 on the acid side and p_H 10 to 11 on the alkaline side.

It is thus possible by administering the starch in a slightly acid solution to do away with any salivary digestion, and digestion will not begin until the acid gastric contents are neutralized in the small intestine. If the salivary enzyme is permanently destroyed by the acid and by its sojourn in the stomach, hydrolysis of the starch will depend almost entirely on pancreatic activity, and on the degree to which the medium in the upper intestine favors the working of the amylase. That these factors are constant in the normal is shown by the uniformity of blood sugar curves following the ingestion of starch by the normal person. Maclean,[4] Gray,[5] and Rowe and Rogers [6] studied

---

* From the University Clinic, Royal Victoria Hospital.

1. Hahn, A., and Meyer, H.: Ztschr. f. Biol. **76**:227, 1922.
2. Willstatter, R.; Leitz, E. W., and Hesse, A. R. F.: Ztschr. f. physiol. Chem. **126**:143, 1923.
3. Sherman, H. C.; Thomas, A. W., and Baldwin, M. E.: J. Am. Chem. Soc. **41**:231, 1919.
4. Maclean, H.: Glycosuria and Diabetes, London, Constable & Co., 1924.
5. Gray, H.: Blood Sugar Standards; Normal Diabetic Persons, Arch. Int. Med. **31**:241 (Feb.) 1923.
6. Rowe, A. H., and Rogers, H.: Carbohydrate Tolerance in Normal Persons and in Nondiabetic Patients, Arch. Int. Med. **39**:330 (March) 1927.

the blood sugar after the feeding of starch, with particular reference to carbohydrate tolerance, and obtained uniform curves. Maclean found curves almost identical with those in which equivalent quantities of dextrose were administered. These investigators did not attempt to eliminate salivary digestion. That the intestinal absorption of dextrose is a fairly constant factor is shown by the uniformity in results of dextrose tolerance tests, so widely employed clinically in recent years.

METHOD

Rabbits were employed in the experiments. After a preliminary starvation of 16 to 24 hours, ten grams of uncooked soluble starch (Merck) were given in suspension in 50 cc. of warm water, to which 0.2 or 0.3 cc. of normal hydrochloric acid was added just before administration. This was given by stomach

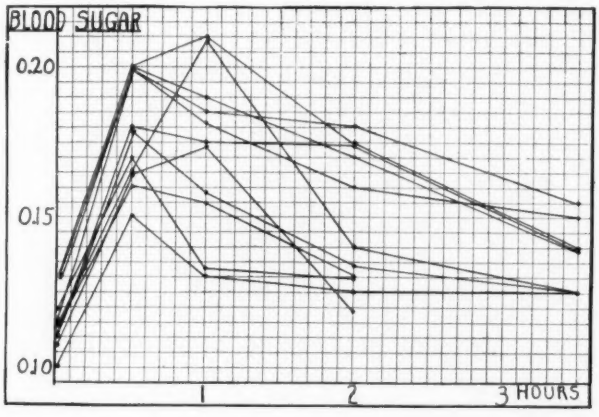


Chart 1.—Blood sugar curves after the administration of 10 Gm. of starch to normal rabbits.

tube and washed in with 10 cc. of water. Samples of blood were taken from an ear vein before and at intervals following the starch feeding, and the blood sugar was estimated by the method of Folin and Wu.

After normal curves were obtained in a series of rabbits, the pancreatic ducts were ligated. Then the tests were repeated after the rabbits recovered from the operation. There is usually only one pancreatic duct in the rabbit, and it enters the duodenum far down, 8 or more inches (20.3 cm.) from the pylorus.

RESULTS

In a series of normal rabbits curves typical of sugar tolerance tests were obtained. The rises in blood sugar varied from 50 to 95 mg. per hundred cubic centimeters of blood with an average of 62 mg. per hundred cubic centimeters of blood. The blood sugar rose rapidly, usually reaching a maximum in one half hour, and then gradu-

ally falling, not quite to normal, within three and one half hours. In two rabbits to which acid was not given with the starch, the blood sugar curves were similar to the others in which 0.2 or 0.3 cc. of normal acid was used.

TABLE 1.—*Blood Sugar Changes after Administration by Stomach Tube of Ten Grams of Uncooked Starch in Fifty Cubic Centimeters of Water to Normal Rabbits* *

Rabbit	Normal Hydrochloric Acid, Cc.	Blood Sugar, Mg. per Hundred Cubic Centimeters of Blood				
		Control	½ Hour	1 Hour	2 Hours	3½ Hours
1.	0.2	133	200	210	174	140
2.	0.2	133	200	185	181	156
3.	0.2	117	200	190	170	138
4.	0.0	133	200	182	160	151
7.	0.0	121	182	157	133	125
10.	0.2	115	166	210	140	125
11.	0.2	118	180	176	176	140
12.	0.2	100	150	130	125	125
16.	0.3	110	160	154	131	...
19.	0.3	108	166	182	111	...
19.	0.3	118	170	133	130	...

* To prevent salivary digestion, 0.2 or 0.3 cc. of normal hydrochloric acid was added.

TABLE 2.—*The Effect of Ligation of the Pancreatic Duct on the Increase in Blood Sugar after Starch Feeding*

Rabbit	Day Before or After Operation	Blood Sugar, Mg. per Hundred Cubic Centimeters of Blood				
		Control	½ Hour	1 Hour	2 Hours	3½ Hours
1.	Before	133	200	210	174	140
	Second after	140	150	146	140	138
2.	Before	133	200	185	181	156
	Second after	116	115	116	118	116
	Fifth after	150	160	160	154	...
	Tenth after	72	72	...	77	70
3.	Before	117	200	190	170	138
	First after	111	114	...	105	102
	Fourth after	125	125	133	133	...
12.	Before	100	150	130	125	125
	Second after	120	120	100	116	110
	Sixteenth after *	114	...	148	130	121
16.	Before	114	160	154	131	...
	Third after	115	138	131	121	...
	Fifth after	111	133	118	118	...
	Seventh after	108	138	133	127	...
19.	Before	118	170	133	130	...
	Before	108	166	182	118	...
	Third after	90	109	133	105	...
	Fifth after	114	153	133	111	...
	Seventh after	127	146	138	125	...

* At autopsy the duct was found patent.

In six rabbits fourteen tests were performed from one to ten days after ligation of the pancreatic duct. Either no rise of blood sugar or an increase of 5 to 10 mg. per hundred cubic centimeters of blood occurred in four of the rabbits. Rabbit 16 had an average rise of 25 mg. per hundred cubic centimeters of blood, and rabbit 20 a rise of 31 mg. per hundred cubic centimeters of blood following ligation of the duct. In rabbit 22 a normal curve was obtained on the sixteenth day; at autopsy it was found that the ligature had dis-

appeared from the pancreatic duct, which was not dilated. Methylene blue injected into it entered freely into the intestine. In the other animals, complete obstruction was demonstrated by the injection of dye into the duct. The presence of minute accessory ducts could not be definitely excluded, although a careful search was made for them at autopsy.

APPLICATION AS A METHOD FOR STUDYING UPPER INTESTINAL DIGESTION

The digestion of starch, when salivary action in the mouth and stomach is eliminated, proceeds in the upper intestinal canal. The rate at which this digestion proceeds can be followed fairly closely by a study of the blood sugar. It seemed likely that in normal persons or in persons in whom there is an adequate secretion of pancreatic amylase such a method would be useful for the investigation

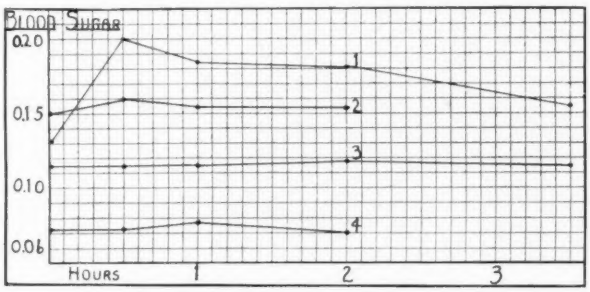


Chart 2.—Effect of ligation of pancreatic duct in rabbit 2: curve 1, before operation; curve 2, five days after operation; curve 3, two days after operation; curve 4, ten days after operation.

of various factors or pathologic states which might influence digestion in the upper part of the small intestine.

In view of the high degree of sensitivity of the pancreatic and intestinal enzymes to hydrogen ions, and in view of the fact that in normal persons the reaction of the upper intestinal contents is frequently not the optimum for their action, an attempt was made to study the effect of the administration of increased quantities of acid on the digestion of starch. The acid was added to the starch solution immediately before it was given by stomach tube to the rabbits. Any hydrolysis of the starch which the acid itself might produce would tend to increase the rise in blood sugar. Since a marked depression was always obtained, this source of error can be neglected. Incubation of soluble starch in eight hundredths normal acid at 37 C. for two hours did not produce an appreciable quantity of reducing sugars.

It was a surprise to find that relatively small quantities of acid could appreciably influence the blood sugar changes. The height and shape of the curve were greatly altered when 1 or 2 cc. of normal hydrochloric acid (3.65 per cent) was added to the starch solution. The total rise of blood sugar in four rabbits averaged in one half hour 25 mg., in one hour 29 mg., in two hours 21 mg. and in three and one half hours, 13 mg. per hundred cubic centimeters of blood. In six experiments in which 3 or 4 cc. of acid was added, the blood sugar increases averaged in one half hour 21 mg., in one hour 18 mg. and in two hours 16 mg. per hundred cubic centimeters of blood. These are striking differences from the averages in eleven experiments, in which from 0.2 to 0.3 cc. of acid or none at all was employed. In these, the increases of blood sugar averaged at one half hour 62

TABLE 3.—*Administration of from One to Four Cubic Centimeters of Normal Hydrochloric Acid with the Starch, Which Markedly Depressed the Rise in Blood Sugar and also Delayed the Return to Normal, Indicating Retardation and Lessened Intensity of Digestion*

Rabbit	Normal Hydrochloric Acid, Cc.	Blood Sugar, Mg. per Hundred Cubic Centimeters of Blood				
		Control	½ Hour	1 Hour	2 Hours	3½ Hours
5.	1	114	133	148	143	143
6.	1	130	160	154	130	130
6.	2	108	125	125	125	117
8.	2	125	162	166	162	140
7.	3	130	142	142	137	...
4.	4	110	125	138	138	138
5.	4	131	154	160	166	166
7.	4	108	154	125	111	...
15.	4	111	122	126	129	...
20.	4	111	130	118	114	...

mg., at one hour 54 mg., at two hours 30 mg. and at three and one half hours 16 mg. per hundred cubic centimeters of blood.

The inhibition of digestion from the acid is greatest during the first half hour. It is generally stated that amylase is not only inactivated but rapidly destroyed by acids, but an investigation of this problem with modern methods has not been found. Owing either to the destruction of the enzyme or to the fact that during the time through which these observations were made the reaction of the intestinal contents was never made sufficiently alkaline to approach the p_H at which amylase works best (p_H 6.8) starch digestion proceeded slowly when acid was given. When more than 2 cc. of acid was used as a rule there was no tendency for the blood sugar curve to drop between the first and third hour following starch feeding.

It now remained to prove that the administration of these quantities of acid did not alter the blood sugar changes produced by feeding of starch, either by causing the food to be retained longer in the stomach or by interfering with the intestinal absorption of the products

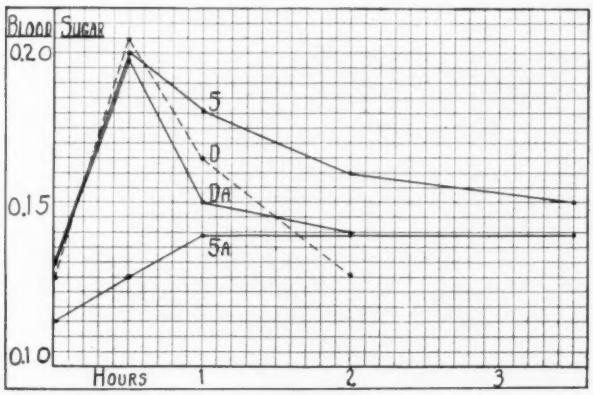


Chart 3.—The inhibition of the upper intestinal digestion by acid in rabbit 4: curve 5, blood sugar after the administration of 10 Gm. of starch + 0.2 cc. of normal hydrochloric acid; curve 5A, after 10 Gm. of starch + 4 cc. of acid; curve D, after 1 Gm. of dextrose (in 60 cc. of water); curve DA, after 1 Gm. of dextrose + 4 cc. of acid.

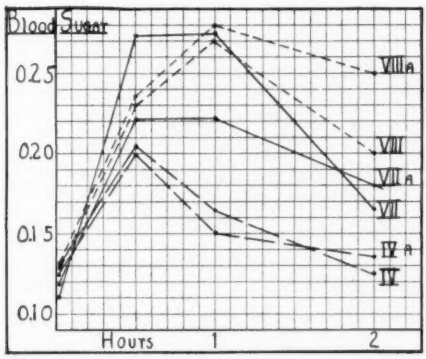


Chart 4.—Showing that acid does not appreciably alter the blood sugar curve after the administration of dextrose: in rabbit 4, 1 Gm. of dextrose with 4 cc. of normal hydrochloric acid; (IV*a*) and without (*IV*; in rabbit 7, 3 Gm. of dextrose + 3 cc. of acid (VII*A*); in rabbit 8, 5 Gm. of dextrose + 4 cc. of acid (VIII*A*).

of starch digestion. This was done by giving to three rabbits 1, 3, and 5 Gm. of dextrose in 50 cc. of water and determining the blood sugar curves. After an interval of several days the tests were repeated, 3 or 4 cc. of normal hydrochloric acid being added to the dextrose solutions. The shapes of the curves with and without acid were almost identical. In rabbit 7 the increase in blood sugar was greater when acid was not given, but in rabbit 8 the reverse tended to hold true. These experiments indicate that in the rabbit from 1 to 2 Gm. of dextrose will produce a blood sugar curve of a magnitude similar to that obtained from 10 Gm. of uncooked starch.

COMMENT

There is an apparent field of usefulness for more refined methods of studying the activity of the external pancreatic secretion. The promising experimental results obtained with the starch tolerance test justify its application to clinical use, and an attempt is at present being made to standardize the procedure for employment in man. Preliminary experiments have shown that in man raw starch is digested so slowly that from 50 to 75 Gm. do not produce an appreciable rise in blood sugar. For this purpose, therefore, cooked starch is being used.

The fact that hydrochloric acid so markedly depresses upper intestinal digestion places gastric hypersecretion in a new rôle which may explain some of the digestive and metabolic disturbances seen in this condition. For it must be remembered that trypsin, erepsin and lipase are similarly susceptible to hydrogen ions, and that what has been found for carbohydrate digestion probably applies to protein and fat digestion also. It is hoped that the carrying out of experiments along similar lines with albumoses and fats will show that this is true.

Calculations based on the secretion of hydrochloric acid in the dog [7] indicate that the rabbit would produce in the neighborhood of from 1 to 4 cc. of normal hydrochloric acid during a meal. A part of this would be combined with the food proteins, but the amounts used do not vary far from physiologic limits.

The bile is an important factor in the neutralization of the acid gastric contents, and intestinal digestion in obstructive jaundice deserves study from this method of approach.

CONCLUSIONS

In a series of ten rabbits, 10 Gm. of uncooked starch in slightly acid solution was administered by stomach tube. A uniform rise in blood sugar resulted, averaging 62 mg. per hundred cubic centimeters of blood.

---

7. Rosemann, R.: Arch. f. Physiol. **118**:467, 1907.

Tests repeated after ligation of the pancreatic duct showed either no rise in blood sugar or an increase of from 5 to 31 mg. per hundred cubic centimeters of blood.

The addition of from 1 to 4 cc. of normal hydrochloric acid to the starch markedly altered the height to which the blood sugar rose in normal rabbits. The shape of the blood sugar curve was also changed, indicating that starch digestion was greatly inhibited during the first hour following its administration, and then proceeded at a slow rate over a period that was much more prolonged than normal. That this was due to the depressing effect of the acid on the activity of the intestinal enzymes was shown by the fact that similar quantities of acid added to solutions of dextrose did not appreciably alter the tolerance for dextrose.

THE ANTAGONISM BETWEEN INSULIN AND PITUITARY EXTRACT

ITS DEMONSTRATION IN A PATIENT WITH ACROMEGALY *

HELMUTH ULRICH, M.D.
Associate Professor of Clinical Pathology, Boston University School of Medicine
BOSTON

The pituitary body has for a long time been known to play a part in the mechanism that controls carbohydrate metabolism. Goetsch, Cushing and Jacobson [1] noted the high carbohydrate tolerance that accompanies pituitary deficiency, and they confirmed Borchardt's [2] previous assertion that the injection of pituitary extract caused hyperglycemia.

Stenström [3] made the apparently conflicting observation that pituitary extract inhibited the hyperglycemia and glycosuria caused by injections of epinephrine hydrochloride. This was afterward confirmed by Burn [4] who was led thereby to speculate that pituitary extract should enhance the action of insulin. He found the opposite to be true,[5] namely, that posterior lobe extract, when injected into rabbits simultaneously with insulin, "had a powerful antagonistic effect on the action of insulin" as well as on that of epinephrine hydrochloride.

Olmstead and Logan,[6] in their work with decerebrated cats, reached the same conclusion, and the studies of Joachimoglu and Metz,[7] Laura,[8] and others added further confirmation.

---

* From the Evans Memorial for Clinical Research and Preventive Medicine.

1. Goetsch, E.; Cushing, H., and Jacobson, C.: Carbohydrate Tolerance and the Posterior Lobe of the Hypophysis Cerebri, Bull. Johns Hopkins Hosp. **22**:165, 1911.

2. Borchardt, L.: Experimentelles über den Diabetes bei der Akromegalie, Deutsche med. Wchnschr. **34**:946, 1908.

3. Stenström, T.: Das Pituitrin und die Adrenalinhyperglykämie, Biochem. Ztschr. **58**:472-482, 1913.

4. Burn, J. H.: Hyperglycemia Produced by Adrenalin and by Anesthesia, J. Physiol., Proc. Physiol. Soc., Jan. 23, 1915, vol. 49.

5. Burn, J. H.: The Modification of the Action of Insulin by Pituitary Extract and Other Substances, J. Physiol. **57**:318, 1923.

6. Olmstead, J. M. D., and Logan, H. D.: The Effect of Insulin on the Central Nervous System and Its Relation to the Pituitary Body, Am. J. Physiol. **66**:437 (Oct.) 1923.

7. Joachimoglu, G., and Metz, A.: Ueber den Antagonismus von Insulin und Hypophysenpräparaten, Deutsche med. Wchnschr. **50**:1787 (Dec. 19) 1924.

8. Laura, L.: Stato presente della teoria pancreatica del diabete a della relazione tra insulina e pituitrina, Riforma med. **41**:582 (June 22) 1925.

Moehlig and Ainslee[9] believed that the antagonism of pituitary extract consisted of a conversion of muscle glycogen to dextrose. Lawrence and Hewlett[10] were of the same opinion. They found, furthermore, that the usual small dose of pituitary extract (1 cc.) inhibited the hypoglycemic effects of insulin given at the same time.

In a different sphere of action, Serebrijski and Vollmer[11] and Koref and Mautner[12] proved that both insulin and pituitary extract, when used separately, reduced the excretion of water by the kidneys; but that this inhibitory action was nullified when they were given together. Then water excretion occurred in a normal manner. And Coope[13] who, with Chamberlain,[14] had previously shown that injections of pituitary extract caused fatty infiltration of the liver of rabbits, discovered that the simultaneous injection of insulin profoundly modified and often prevented this effect. This suggests that the antagonism between these hormones is not one-sided, that is, of pituitary extract against insulin only, but reciprocal.

All of the quoted experimental research indicates that loss of carbohydrate tolerance in hyperpituitary disease is due to an antagonistic inhibitory action, exercised by excessive pituitary secretion, probably of the posterior lobe, on normal insulin function. If this assumption is correct, then the use of insulin in the treatment of patients with hyperpituitary glycosuria should prove partially or wholly ineffective.

Falta[15] reported the case of an insulin refractive patient with glycosuria, whose low basal metabolic rate, obesity and extremely small sella suggested to him a hypophysial influence. In the case of Mahler and Pasterny,[16] the patient had a proved pituitary tumor. Sixty units of insulin did not affect the hyperglycemia.

---

9. Moehlig, R. C., and Ainslee, H. B.: Antagonistic Action of Posterior Pituitary Extract and Insulin, J. A. M. A. **84**:1398 (May 9) 1925.

10. Lawrence, R. D., and Hewlett, R. F. L.: The Effect of Pituitrin and Insulin on Blood Sugar, Brit. M. J. **1**:998 (May 30) 1925.

11. Serebrijski, F., and Vollmer, H.: Zum Antagonismus zwischen Insulin und Hypophysenhormon, Klin. Wchnschr. **4**:2256 (Nov. 19) 1925.

12. Koref, O., and Mautner, H.: Ueber den Einfluss von Pituitrin und Insulin auf den Wasserhaushalt, Mon .tschr. f. Kinderh. **31**:303, 1925.

13. Coope, R.: Insulin and Pituitrin "Fat Liver," J. Physiol. **60**:92 (May) 1925.

14. Coope, R., and Chamberlain, E. N.: The Effect of Pituitrin on the Fatty Acid of the Liver, J. Physiol. **60**:69, 1925.

15. Falta, W.: Ueber einen insulinrefraktären Fall von Diabetes mellitus, Klin. Wchnschr. **3**:1315 (July) 1924.

16. Mahler, P., and Pasterny, K.: Klinische Beobachtungen über Insulinwirkung beim Diabetes mellitus, Med. Klin. **20**:337 (May 16) 1924.

Cushing,[17] John[18] and Hetzel,[19] however, stated, in effect, that pituitary diabetes does not differ from pancreatic diabetes in its response to insulin therapy. Cushing has apparently come to a different conclusion, because in a recent paper of his, written jointly with Davidoff,[20] the belief is expressed that insulin may be less effective in patients with pituitary glycosuria than in those with pancreatic diabetes. John's two case reports, one of which will be discussed later, are not convincing and lend themselves readily to an entirely different interpretation. Hetzel's case, too, will be taken up again, and, according to Hetzel's own words, the patient will be shown to have been refractory to insulin, despite the conclusion that insulin treatment was effective.

The following study of a patient with acromegaly and hyperglycemia is presented in support of the quoted laboratory evidence that antagonism between pituitary extract and insulin exists and may be clinically demonstrable.

REPORT OF CASE

L. D. C., a man, aged 24, was admitted to the Evans Memorial Hospital on July 3, 1924, for endocrine study. A diagnosis of pituitary neoplasm was made, based on the presence of headache, characteristic changes in the ocular fundi and color fields, a basal metabolic rate of minus 11 and an enlarged sella turcica with a shallow and eroded floor. At this time glycosuria was not found. He was discharged in two weeks, and readmitted a month and a half later, complaining particularly of headache. Glycosuria was absent.

The patient's next entry was on Dec. 13, 1924, when he complained of marked thirst, polyuria and weakness. Glycosuria was now present, the sugar in the urine amounting to 238 Gm. in twenty-four hours.

In view of Cushing's[17] statement that "we know that acromegalic glycosuria is associated with a hyperglycemia, and that it reacts to insulin as does pancreatic diabetes," difficulty was not expected in the attempt to control glycosuria in this patient.

He was given 10 units of insulin before each meal and a diet containing approximately 80 Gm. of protein, 160 Gm. of fat and 60 Gm. of carbohydrate (chart 1). The blood sugar was 404 mg. per hundred cubic centimeters of blood. After two days of insulin treatment, the urine sugar was 81.8 Gm. This was a satisfactory reduction, but, to hasten results, the amount of insulin was doubled. The blood sugar did not decrease but increased to 500 mg. The dosage of insulin was increased to 40 units three times a day, but the blood sugar increased further to 625 mg. This led to another doubling of insulin dosage to 80 units before each meal. Glycosuria decreased, the sugar in the urine amounting to 40 Gm., and the blood sugar to 285 mg.; nevertheless, the dosage of insulin was increased to the huge amount of 120 units three times a day. Glycosuria

17. Cushing, H.: The Pituitary Gland as Now Known, Lancet **2**:899 (Oct. 31) 1925.

18. John, H. J.: The Possible Relationship Between Acromegaly and Diabetes, Arch. Int. Med. **37**:489 (April 15) 1926.

19. Hetzel, K. S.: Glycosuria in Acromegaly, Lancet **1**:440 (Feb. 27) 1926.

20. Davidoff, L. M., and Cushing, H.: Studies in Acromegaly: VI. The Disturbances of Carbohydrate Metabolism, Arch. Int. Med. **39**:751 (June) 1927.

decreased until there was only a trace of sugar in the urine, and the blood sugar decreased to 154 mg.

It was deemed hazardous to continue the high dosage of insulin at this relatively low level of blood sugar; therefore, a reduction to 80 units three times daily was made. Sugar disappeared from the urine on the following day. The dosage of insulin was gradually reduced to 60, 40, 20 and 10 units, and finally was omitted. Blood sugar had steadily receded, despite this reduction of insulin dosage, until it reached 87 mg. on January 30, three days after insulin therapy had been stopped.

Throughout this time the patient had been given the diet referred to previously, but when the blood sugar fell to 87 mg., a nondiabetic diet was ordered. Sugar did not reappear in the urine, except a trace on April 4 and 0.2 per cent on June 20. The blood sugar remained low for five months. It amounted to 126 mg. on June 19, two days before the patient's discharge.

He was readmitted on July 25, 1925, because of recurring headache. The urine contained no sugar and the blood was normal. He left the hospital on

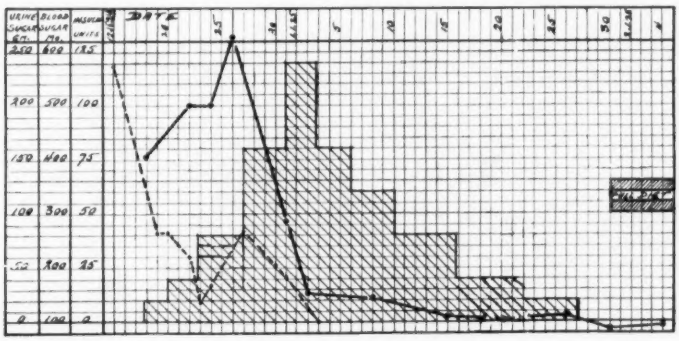


Chart 1.—The solid line depicts blood sugar; the broken line, sugar in the urine; and the hatched area, amounts of insulin per dose. A diabetic diet was given throughout this period, except when unrestricted diet is indicated.

November 15, and reentered a week later. The blood sugar amounted to 142 mg. The patient's progress was not favorable, headache being particularly troublesome, so that surgical intervention was decided on.

After operation, both glycosuria and hyperglycemia reappeared in marked degree and increased steadily for a month. It is possible that these postoperative manifestations were due, in part, at least, to the injury of contiguous cerebral tissue. Insulin in 40 unit doses had a definite depressing effect on this traumatic hyperglycemia, reducing it in twelve days from 500 mg. to 167 mg. Later, however, presumably after the subsidence of the operative effects and reassertion of hyperpituitary activity, evidence of insulin failure was again demonstrable; but the slight hyperglycemia (125 mg.) found at this time gave less striking results. The patient was discharged, showing daily traces of sugar in the urine and persistent slight hyperglycemia.

He was admitted again on Nov. 30, 1926, with 286 mg. of blood sugar and 111 Gm. of sugar in the urine. Four days later, the blood sugar was unchanged. Then it increased to 363 mg. Twenty units of insulin, given three times a day, lowered the amount of sugar in the urine, but the blood sugar remained

unaffected. Insulin was then discontinued, and dietetic restrictions were removed. The blood sugar promptly increased to 500 mg. These effects and others caused by changes of diet and variations in the dosage of insulin are depicted on chart 2, which covers the period of his stay in the hospital.

Analysis of charts 1 and 2 must lead to the conclusion that insulin had but little effect on the blood sugar level of this patient during the periods covered by these charts. (The postoperative hyperglycemia, which may have been due to surgical trauma, appeared to be more responsive.) One should note, particularly, in the first half of chart 1, the increasing blood sugar while insulin was being increased and, in the second half of this chart, the persistent decline of hyperglycemia, despite a fairly rapid decrease in the dosage of insulin from the huge total of 360 units a day to nothing. At first glance it may appear that

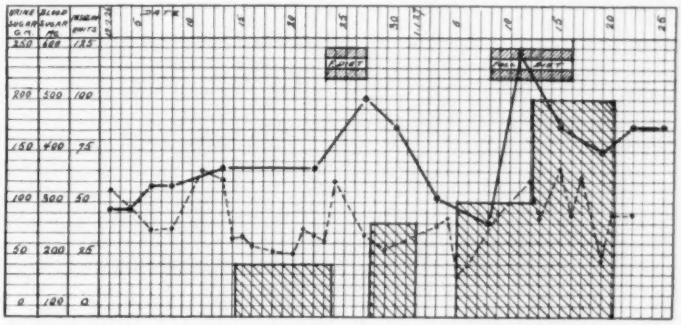


Chart 2.—Blood sugar variations are indicated by the solid line, glycosuria by the broken line. The dosage of insulin is shown by the large hatched blocks. A diabetic diet was given throughout, except as indicated.

insulin treatment was responsible for this lowering of the blood sugar level. Closer study of the chart disproves this. It should be noted especially that without insulin, even with unrestricted diet, the blood sugar remained normal.

It is known that glycosuria accompanying hyperpituitary disease may disappear spontaneously, regardless of treatment. John [21] and Hetzel [19] reported cases of acromegaly, previously cited, in which this occurred. Indeed, their cases seem to be similar to the one reported here. But John believed that the elimination of glycosuria in his patient was due to dietetic restrictions and the use of insulin and that the case was one of cured pancreatic diabetes. Hetzel came to the conclusion that in his patient "The glycosuria was identical with that of diabetes, it

21. John, H. J.: Spontaneous Disappearance of Diabetes, J. A. M. A. **85**:1629 (Nov. 21) 1925.

reacted similarly to insulin and control of the diet." This conclusion, however, does not agree with the text of his case report. There he stated that "the efficacy of insulin was doubtful" and that it "had only a small effect on the blood sugar."

To be sure, in his case as in John's, all evidences of diabetes finally vanished, and it may have been this fact that brought Hetzel to the foregoing conclusion. But insulin does not act in that way. Its intensive use, as has been shown,[22] may raise the carbohydrate tolerance of children and young adults a little, but it does not cure diabetes. Both Hetzel and John were apparently misled, in that they misinterpreted a spontaneous recession of pituitary hyperglycemia as an effect produced by insulin.

Sachs and MacDonald[23] reported the case of a woman who was operated on for "acute acromegaly." The operation was followed by glycosuria which, they stated, "in no way differed from glycosuria of a diabetic patient," and which "was furthermore controlled by administration of insulin." Glycosuria was apparently not present before operation, so that in this patient it must be regarded as a result of operative trauma rather than as a symptom of pituitary disease. This places the case in an entirely different category and does not prove the efficacy of insulin in true hyperpituitary glycosuria.

The only seemingly valid evidence of efficient insulin action in this type of glycosuria is furnished by Blum and Schwab.[24] They gave 30 units of insulin to each of two patients, one suffering from acromegalic glycosuria, and the other from pancreatic diabetes. The responses were essentially equal.

This may mean that there are gradations of antagonism in different patients with hyperpituitary disease, ranging in intensity from none at all, as in the case of Blum and Schwab, to almost complete inhibition, as in my case. Or, if it is true that pituitary tumors may give rise to glycosuria by pressure on neighboring brain centers, the simultaneous presence of this pressure type, which may be amenable to insulin, with a hypersecretory type, would lead to varying degrees of responsiveness to treatment with insulin. Again, it is conceivable that some of the patients may develop true pancreatic diabetes, owing to exhaustion of the pancreas from constant stimulation by the pituitary

22. Ulrich, H.: Induced Hypoglycemia as a Means of Resting and Improving Pancreatic Function in Patients With Diabetes, J. A. M. A. **83**:1914 (Dec. 13) 1924.

23. Sachs, E., and MacDonald, M. E.: Blood Sugar Studies in Experimental Pituitary and Hypothalamic Lesions, Arch. Neurol. & Psychiat. **13**:335 (March) 1925.

24. Blum, L., and Schwab, H.: Diabète acromégalique et insuline, Compt. rend. Soc. de biol. **89**:195 (June 8) 1923.

hyperglycemia. Such patients may then become more susceptible to treatment with insulin.

Chart 2 shows clearly that the hyperglycemia of my patient was influenced markedly by dietetic changes, and the second half of this chart suggests that insulin also had a slight effect. To ascertain more definitely the direct action of insulin, uncomplicated by dietetic influence, large doses were given before breakfast on four widely separated days, as illustrated on chart 3. On each of three of these occasions the amount of insulin was 50 units, and on one it was 100 units. Blood sugar determinations were made at varying intervals after the injections of insulin. Food was not allowed until after the last specimen of blood of that day had been drawn. Similar tests, to serve as controls, were conducted with four patients suffering from so-called pan-

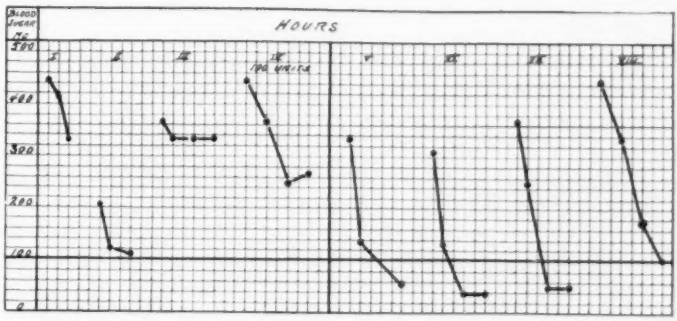


Chart 3.—Changes in the blood sugar level following injections of insulin, with the patients in the fasting state. The amount of insulin given was 50 units in each instance, except in experiment IV, when 100 units was used. Curves I to IV represent the blood sugar responses of the patient with acromegaly. Curves V to VIII show the responses of four patients with pancreatic diabetes. The first blood sugar value in each case was obtained immediately before the injection of insulin; the others, as shown on the chart, at varying intervals afterward.

creatic diabetes. The curves depicting these tests are plotted at the right of chart 3.

In the patient with acromegaly, the injection of insulin was followed in at least three of the four tests by a definite lowering of the blood sugar level. If curve I had been extended, it might possibly have shown a further depression of glycemia. Aside from this possibility, however, a comparison of the two sets of curves shows decidedly different results. The extent of the reduction of blood sugar was much greater in the patients with pancreatic diabetes. Three of them became markedly hypoglycemic and developed symptoms of severe insulin shock.

Comparison of curves IV and VIII is particularly instructive. Both show blood sugar values of 444 mg. before the injection of insulin. The patient with acromegaly received 100 units and responded with a decrease to 250 mg.; the patient with diabetes received only 50 units, but the decrease in his blood sugar was more than twice as great.

SUMMARY

1. Medical literature contains much experimental evidence that the internal secretion of the posterior pituitary lobe antagonizes insulin.

2. A case of hyperpituitary disease with acromegaly and glycosuria is reported, in which this antagonistic action is demonstrated.

3. The opinion is expressed that this antagonism may vary in different patients.

4. Insulin may, therefore, show varying degrees of efficiency in the treatment of hyperpituitary loss of carbohydrate tolerance.

5. In the case reported, its effectiveness was much impaired.

ACROMEGALY AND DIABETES

REPORT OF SIX CASES *

WALLACE M. YATER, M.D.
Fellow in Medicine, The Mayo Foundation
ROCHESTER, MINN.

It is assumed in this paper that acromegaly is a constitutional disease of adult life due to overactivity of the anterior lobe of the pituitary gland, manifest pathologically by a hyperplastic or adenomatous process composed of acidophilic cells.[1] Since the first comment on the frequent occurrence of mellituria in persons with tumor of the hypophysis, made by Loeb[2] in 1884, there has been much experimentation and much discussion concerning the relationship of the pituitary gland to the diabetes. The hypotheses thus far advanced are:

1. In the hypothalamus in the neighborhood of the hypophysis, there is a center which regulates carbohydrate metabolism. In acromegaly, the pressure of a large tumor of the pituitary gland on this center causes the diabetes.

2. The glycosuria is due to secondary changes in the pancreas

3. There is a disturbance of the internal secretion of the thyroid gland, which impairs the functional ability of the islands of Langerhans.

4. An excess of secretion of the posterior lobe of the pituitary gland itself is responsible for the diabetes, probably by stimulating glycogenolysis in the glycogen reservoirs and thus supplying glucose at a rate beyond the ability of the tissues to utilize it.

5. The hypophysis itself contains nerve centers or tracts which are effective in producing such an excessive glycogenolysis.

6. The hypophyseal secretion or a nerve center in or near the hypophysis serves to check the rate of secretion of insulin from the islands of Langerhans.

---

* Work done in the Division of Medicine, Mayo Clinic, under the direction of Russell M. Wilder.

1. Bailey, Percival, and Davidoff, L. M.: Concerning the Microscopic Structure of the Hypophysis Cerebri in Acromegaly, Am. J. Path. **1**:185, 1925. Cushing, Harvey, and Davidoff, L. M.: Studies in Acromegaly: V. The Pathological Findings in Four Autopsied Cases of Acromegaly with a Discussion of their Significance, Monograph, New York, Rockefeller Inst. Med. Res., 1927, vol. 22.

2. Loeb, M.: Ein Erklarungsversuch der verschiedenartigen Temperaturverhältnisse bei der tuberculösen Basilarmeningitis, Deutsches Arch. f. klin. Med. **34**: 443, 1884.

7. The internal secretion of the pituitary gland is directly antagonistic to insulin and nullifies its effect.

The results of experimental and clinical investigations regarding the relationship of the pituitary gland to carbohydrate metabolism may be summarized as follows:

1. Acromegaly is found to be complicated by diabetes mellitus more frequently than by any other disease. It has been estimated in various series of cases of acromegaly that diabetes occurs in from 9 to 40 per cent, with an average, probably, of from 10 to 12 per cent. These figures are subject to two errors: In many cases, the diagnosis of diabetes rests on insufficient data, such as the presence of glycosuria alone; in other cases, the patients were not examined sufficiently often or followed long enough to justify any conclusions as to whether diabetes had been present or would develop. Nevertheless, the frequency is so striking as to suggest more than an accidental relationship. Borchardt,[3] tabulating the cases from the literature up to 1908, found that there were 63 (35.5 per cent) which were complicated by frank diabetes and 8 more which were associated with at least an alimentary glycosuria. Davidoff [4] reported that in 25 of Cushing's 100 cases of acromegaly mellituria was evident and that in 12 of these frank diabetes was present.

2. Glycosuria and diabetes are uncommon in nonacromegalic disorders of the hypophysis, such as tumors of the hypophysis itself not accompanied by acromegaly and lesions in the vicinity of the hypophysis which cause pressure on the gland or invade it secondarily. Colwell,[5] however, found, even after an incomplete survey, 38 cases of nonacromegalic disorders of or near the hypophysis accompanied by glycosuria or diabetes, and suggested that this number compares favorably with the incidence of glycosuria or diabetes in patients with acromegaly.

3. Hypopituitarism is rarely associated with glycosuria; increased tolerance is a usual occurrence. The syndrome of obesity, delayed development of the sexual organs and functions, lack of secondary sex characteristics and inferior mental capacity, has been assigned to a deficiency of pituitary secretion because of the demonstration in such cases of destructive lesions involving the hypophysis and because of the experimental production of such a syndrome by extirpation of

3. Borchardt, L.: Die Hypophysenglykosurie und ihre Beziehung zum Diabetes bei der Akromegalie, Ztschr. f. klin. Med. **66**:332, 1908.

4. Davidoff, L. M.: Studies in Acromegaly: III. The Anamnesis and Symptomatology in One Hundred Cases, Endocrinology **10**:461, 1926.

5. Colwell, A. R.: The Relation of the Hypophysis to Diabetes Mellitus, Medicine **6**:1, 1927.

the hypophysis in animals. Goetsch, Cushing and Jacobson,[6] especially, have been responsible for this view and have demonstrated the increased tolerance for carbohydrates in such cases. These investigations also showed that hyperglycemia induced by removal of a large portion of the pancreas tended to subside when partial hypophysectomy was later performed; and, conversely, that when animals had acquired a high sugar tolerance with hypoglycemia after hypophysectomy, they bore the removal of a large portion of the pancreas with less disturbance of carbohydrate balance than the normal animal would. This work and that of others has been criticized, however, because the alimentary glucose tolerance test was used. Moreover, Gibson [7] reported a typical example of hypopituitarism in which diabetes existed, and John [8] reported 5 cases of clinical hypopituitarism with glycosuria or decreased sugar tolerance (oral method of administration), which represented 12 per cent of the cases of hypopituitarism at the Cleveland Clinic. However, in the entire series of 185 cases from the Peter Bent Brigham Hospital in which the diagnosis of pituitary tumor recorded as "chromophobe" was verified histologically, only 4 were proved to have been associated with even transient glycosuria. Wilder and Sansum,[9] giving glucose intravenously continuously and at a constant rate in 2 patients with Frölich's syndrome, observed essentially the same limit of assimilation as in 4 normal controls. They concluded that the increased tolerance demonstrated by those who used the oral method might have been due to some such factor as delayed absorption.

4. Transient glycosuria follows removal of the hypophysis in animals (first shown by Caselli,[10] in 1900 and by Friedman and Maas [11] in the same year, and confirmed by many other investigators). Goetsch, Cushing and Jacobson [6] found that any operative manipulation of the gland would frequently cause glycosuria. Weed, Cushing and Jacobson [12] observed that direct mechanical or electrical manipulation of the

6. Goetsch, Emil; Cushing, Harvey, and Jacobson, Conrad: Carbohydrate Tolerance and the Posterior Lobe of the Hypophysis Cerebri, Bull. Johns Hopkins Hosp. **22**:165, 1911.

7. Gibson, H. J. C.: Hypopituitarism Associated with Glycosuria, Edinburgh M. J. **31**:82, 1924.

8. John, H. J.: Spontaneous Disappearance of Diabetes, J. A. M. A. **85**: 1629 (Nov. 21) 1925; The Possible Relationship between Acromegaly and Diabetes, Arch. Int. Med. **37**:489 (April) 1926.

9. Wilder, R. M., and Sansum, W. D.: d-Glucose Tolerance in Health and Disease, Arch. Int. Med. **19**:311 (Feb.) 1917.

10. Caselli, A., quoted by Colwell (footnote 5).

11. Friedman, F. F., and Maas, Otto: Ueber Extirpation der Hypophysis cerebri, Berl. klin. Wchnschr. **37**:1213, 1900.

12. Weed, L. H.; Cushing, Harvey, and Jacobson, Conrad: Further Studies on the Rôle of the Hypophysis in the Metabolism of the Carbohydrates, Bull. Johns Hopkins Hosp. **24**:40, 1913.

hypophysis of rabbits, cats and dogs under ether anesthesia invariably produced glycosuria (provided the liver contained sufficient glycogen). They demonstrated, also, that glycosuria followed mechanical or faradic stimulation of the superior cervical sympathetic ganglions and did so even after all of the known nerve paths to the viscera had been severed. They observed that glycosuria did not take place following stimulation of the superior cervical ganglion when the posterior lobe of the hypophysis had previously been removed. They thought that these results showed that the secretion of the posterior lobe itself and not direct stimulation of the liver by a nerve route was responsible for the glycosuria. The work, however, has never been confirmed.

5. In 1909, Aschner [13] provoked glycosuria in an animal for two days by injury to the hypothalamic region in the floor of the third ventricle. In 1912,[14] he reported studies showing that glycosuria was almost always caused by injury of the tuber cinereum. This result was confirmed by others. Camus, Gournay and Le Grand [15] were able to produce prolonged glycosuria by injury of this organ, and in one animal it lasted forty-seven days. Sachs and MacDonald [16] showed that when the base of the brain was not injured during hypophysectomy, glycosuria did not occur, but that it did so only when the brain region of the floor of the third ventricle was injured whether the hypophysis was removed or not.

6. Injection of pituitary extracts often produces transitory glycosuria and hyperglycemia. This has been demonstrated by many investigators, but a few have failed to confirm it.

7. Goetsch, Cushing and Jacobson [6] observed that the high sugar tolerance of some of their animals (alimentary test), even when accompanied by hypoglycemia, could be overcome and glycosuria provoked by the hypodermic injection of anterior lobe as well as posterior lobe extracts. Houssay and Magenta [17] reported that dogs, after the establishment of hypopituitarism by hypophysectomy, were more easily rendered hypoglycemic by the injection of insulin than normal dogs.

---

13. Aschner, Bernhard: Ueber das "Stoffwechsel- und Eingeweidecentrum im Zwischenhirn" seine Beziehung zur inneren Sekretion (Hypophyse, Zirbeldrüse) und zum Diabetes insipidus, Berl. klin. Wchnschr. **2**:772, 1916.

14. Aschner, Bernhard: Ueber die Funktion der Hypophyse, Arch. f. d. ges. Physiol. **146**:1, 1912.

15. Camus, J.; Gournay, J. J., and LeGrand, A.: Diabète sucre expérimental, Comp. rend. Acad. d. sc. **177**:146, 1923.

16. Sachs, Ernest, and MacDonald, M. E.: Blood Sugar Studies in Experimental Pituitary and Hypothalmic Lesions with a Review of Literature, Arch. Neurol. & Psychiat. **13**:335 (March) 1925.

17. Houssay, B. A., and Magenta, M. A.: Sensibilité des chiens hypophysectomises à leigaid de l'insuline, Comp. rend. Soc. de Biol. **92**:822, 1925.

All of the hypophysectomized dogs had convulsions and died, whereas the control animals did not have convulsions and survived. Other investigators, however, have demonstrated the same increased sensitivity to insulin following injury of the infundibulum alone. Olmstead and Logan [18] were unable to produce any substantial reduction of blood sugar by the injection of insulin in decerebrate cats only when the hypophysis was left intact, but demonstrated severe insulin reactions with hypoglycemia and convulsions when the hypophysis was removed with the cerebrum.

8. Burn [19] demonstrated in animals that pituitary extract is capable of preventing and relieving hypoglycemia and convulsions produced by the injection of insulin. Three of Davidoff and Cushing's [20] patients, who had been shown to respond normally to insulin, did not respond as expected (insufficient fall in blood sugar concentration) when 20 units of insulin were combined with 1 cc. of pituitary.

9. Stenström [21] found that pituitary inhibited the hyperglycemia due to the administration of epinephrine, and Aschner [14] observed that the glycosuric effect of epinephrine in hypophysectomized dogs was less constant than in normal animals.

10. The results of hypophysectomy in man have not satisfactorily demonstrated amelioration of the diabetes. It is true, however, that it is extremely difficult to remove all of the gland, and also that the patients have not been sufficiently carefully observed after operation in the majority of cases. Davidoff and Cushing [20] reported only one instance from 14 cases of acromegaly and diabetes in which there was immediate cessation of the glycosuria after operation for pituitary adenoma. Three days after operation the blood sugar content was 0.12 per cent, and glycosuria was not present during the following month up to the time of dismissal. In view of the fact that the pre-existing diabetes had been mild and only recently discovered, and that while in the hospital the patient may not have been consuming as much carbohydrate food as previously, this case is not satisfactory proof of any causal relationship of the pituitary condition to the diabetes. Ellis [22] reported a case in which he claimed that the diabetes

18. Olmsted, J. M. D., and Logan, H. D.: The Effect of Insulin on the Central Nervous System and its Relation to the Pituitary Body, Am. J. Physiol. **66**:437, 1923.

19. Burn, J. H.: The Modification of the Action of Insulin by Pituitary Extract and other Substances, J. Physiol. **57**:318, 1923.

20. Davidoff, L. M., and Cushing, Harvey: Studies in Acromegaly: VI. The Disturbances of Carbohydrate Metabolism, Arch. Int. Med. **39**:751 (June) 1927.

21. Stenström, Thor: Das Pituitrin und die Adrenalinhyperghykämie, Biochem. Ztschr. **58**:472, 1914.

22. Ellis, A. W. M.: Hyperglycaemia and Glycosuria in Acromegaly with Pathological Report by Prof. H. M. Trumbull, Lancet **1**:1200, 1924.

was relieved following hypophysectomy, but three years after the radical extirpation of a pituitary adenoma, the fasting blood sugar content was 0.18 per cent and the glucose tolerance test gave a definitely diabetic curve, although the diabetes for some time following the operation was less intense. The patient, however, had been on a diabetic regimen.

Davidoff and Cushing [20] tested the glucose tolerance in 9 patients with acromegaly, using the intravenous method, before and after hypophysectomy; in 4, a distinct improvement in tolerance was evidenced by a decrease in the blood sugar level. In all but 1 of these 4 cases, there had not been any clinical evidence of diabetes before operation; in 1, mild clinical diabetes was present. In the case in which greatest improvement in tolerance was manifested, the operation was the most radical; in those in which improvement was the least marked the least tissue was removed. Davidoff and Cushing also called attention to the fact that these patients before operation and a few others who were not operated on gave tolerance curves in which the blood sugar rose to a higher level than the normal and, with a single exception, remained higher than the normal throughout the period of examination. One of John's [8] patients, also, did not show glycosuria, but "there was a slight leaning toward impairment of carbohydrate function," as shown by a glucose tolerance test.

11. The diabetes occurring in persons with acromegaly is in all essential respects similar to the diabetes in the absence of acromegaly. John [8] stressed this point with 2 case reports, and Colwell [5] reported a carefully studied case in which this statement was substantiated. In most cases, polydipsia and polyuria have been proportionate to the severity of the diabetes. These symptoms and the glycosuria respond to dietetic management, as in ordinary diabetes. The glycosuria may be intermittent and detectable only after excessive ingestion of carbohydrate. The diabetes is often relatively mild, but some patients have succumbed to diabetic coma. It has often been stated that the diabetes complicating acromegaly runs an irregular course. Colwell studied the literature carefully with this point in mind and collected reports of 17 cases in which an atypical course was claimed to occur. He concluded that in some of these, dietetic control had not been established. In others there appeared to have been a bona fide improvement in the diabetes, and in a few an apparently spontaneous disappearance of the diabetes. Cushing [6] has been an ardent advocate of the theory "that in the early stages of acromegaly the sugar tolerance test is apt to be low but that later in the disease there is an acquired overtolerance;" this is a clinical observation based mainly on the results of tolerance tests for sugar as estimated by the amount necessary to produce glycosuria when taken by mouth. The diabetes associated with acromegaly

responds to insulin as it does in the ordinary form. Several of the cases in the present series demonstrate this point clearly; the subject will be discussed further.

In a series of 79 patients with acromegaly examined at the Mayo Clinic, glycosuria has been observed in 8. Many of the 79 patients were examined on only one occasion. Six of those who manifested glycosuria were studied from the standpoint of the diabetes sufficiently to establish the diagnosis of true diabetes mellitus. Of the other 2 cases, glycosuria was present in one to the extent of 0.8 per cent on one urinalysis only; in the second, 800 cc. of urine contained 11.36 Gm. of glucose (1.37 per cent) and the blood sugar was 180 mg. per cent, but there was no sugar in the urine in a test made one week later. The 6 cases that were more carefully studied are reported in this paper. The authenticity of the acromegaly in one of these (case 4) may be questioned. The history of enlargement of the acral parts and features was lacking and signs of pressure were not present. However, the appearance of the patient was so striking as to suggest acromegaly at once to all the clinicians who saw her. The enlargement of the sella turcica roentgenoscopically further strengthened the impression. The pathologist could not state definitely that the condition was or was not acromegaly, but he admitted that the pituitary gland was larger than normal and showed signs of increased activity as well as several small chromophilic adenomas and an occasional mitotic figure. Insulin was employed in the treatment of 3 of the 6 patients, and, because of the scarcity of reports of cases in which the effects of insulin on the diabetes have been observed, two of these are recorded in some detail.

Two other cases in which frank diabetes was not evident deserve brief mention. In one a hyperfunctioning adenomatous thyroid was present, and the oral administration of 100 Gm. of glucose was followed by a diabetic blood sugar curve; thyroidectomy was performed, but a further study of the blood sugar was not made. In the other, a case complicated by exophthalmic goiter, glycosuria was discovered during preparation for thyroidectomy; 55 units of insulin was given daily, although the only estimations of blood sugar before that time revealed a level of 83 and 125 mg. per cent. The insulin was continued for four days after thyroidectomy; glycosuria was not evident thereafter.

REPORT OF CASES

CASE 1.—*Acromegaly of more than fifteen years' duration with greatly enlarged sella turcica, but without signs of pressure; diabetes mellitus of ten years' duration, easily controlled by diet alone.*

On June 13, 1925, a laborer, aged 49, appeared for examination at the Mayo Clinic with the complaints of diabetes, headaches and impaired vision. The

family history was irrelevant. He was a widower with two children living and well. He had had diphtheria at the age of 6 and influenza in 1918; at one time a nasal operation had been performed, the details of which were not obtainable. Acromegaly had been diagnosed fifteen years before, and he had noticed enlargement of the hands a year prior to that. The acromegaly had gradually progressed since that time. He had suffered from dull bilateral and supra-orbital headaches for twenty years, but these were not as severe as formerly. He had been well otherwise until ten years before admission, when he began to drink about a gallon and a half of water daily; the polydipsia was accompanied by polyuria and polyphagia. Glycosuria had not been discovered until five years later, and since then thirst or polyuria had not been present when the patient was on a qualitative restriction of carbohydrates. Glycosuria had been present during the last five years whenever the urine had been examined. There had not been any loss of weight. For the last fourteen months, the patient had not been careful in the matter of diet, but had taken from 5 to 15 units of insulin, "double strength," each morning. There had been some blurring of vision for the last ten years and loss of sexual desire for the same length of time. General weakness had prevented the patient from working during the last five years. He had complained of dizziness for two or three years, numbness of both legs from the knees down for two years and a running sore on the right great toe for one year.

The patient was large, being 6 feet 2 inches (188 cm.) tall and weighing 242 pounds (110 Kg.). There was general overgrowth of the skeleton, including especially the frontal eminences, the zygomatic processes, malar and nasal bones, the lower jaw and the hands and feet. The teeth were separated. The skin and subcutaneous tissues were thickened, and the skin was dry and scaly. The eyelids were thickened. There were multiple pigmented nevi scattered over the body, especially on the back. There was a foul smelling "trophic" ulcer over the outer surface of the first right metatarsophalangeal joint. The teeth were in bad condition. The tonsils were enlarged and contained liquid pus. The thyroid gland was small, but was palpable, firm and slightly nodular. The heart was moderately enlarged to the left, with a soft systolic murmur at the apex and an occasional premature contraction. The blood pressure was 130 systolic and 74 diastolic; the pulse rate was 74 and the temperature, 98.4 F. The abdomen was pendulous and the liver moderately enlarged. The gait was moderately ataxic. The right adductor pollicis and hypothenar eminence were atrophied. There was some diminution of sensation below the knees. The reflexes were present but sluggish. Both great toes showed a tendency to go into plantar extension. Vision in the right eye was 6/10 and in the left 6/5. The light reflex was somewhat cut down in both eyes. There was moderate retinitis of mixed diabetic and vascular types. The visual fields were normal.

Urinalysis showed a specific gravity of 1.041; acid reaction; no albumin; 2.4 per cent sugar, with 27.5 Gm. in 1,100 cc. (twelve-hour specimen); no acetone or diacetic acid, and negative microscopic examination. The hemoglobin was 75 per cent; the erythrocytes numbered 4,530,000 and the leukocytes, 6,600. The blood urea was 30 mg. per cent and the blood sugar, 300 mg. per cent. The Wassermann reaction was negative. A roentgenogram of the skull showed the sella turcica greatly enlarged and destruction of the floor (fig. 1). An electrocardiogram showed a rate of 82, left ventricular preponderance, slurred Q. R. S. complex in leads I and II, occasional ventricular premature contractions, inverted P in lead III and inverted T in lead III. Two basal metabolic rates were +7 and +6.

The condition was diagnosed as acromegaly with pituitary tumor and diabetes mellitus with diabetic neuritis and a trophic ulcer.

For the first ten days, the patient was given a diet containing 28 Gm. of carbohydrate, 43 Gm. of protein and 175 Gm. of fat (1,920 calories, 71 Gm. of glucose[23]). For the next five days the diet contained 94 Gm. of carbohydrate, 55 Gm. of protein, and 242 Gm. of fat (2,850 calories, 150 Gm. of glucose). Sugar was not found in the urine after the second day. The blood sugar on the second day was 237 mg. per cent and on the eighth day, 143 mg. per cent.

Fig. 1 (case 1).—Lateral roentgenographic appearance of the skull showing the enlarged sella turcica.

CASE 2.—*Acromegaly of from fifteen to twenty years' duration without signs of pressure and diabetes mellitus without symptoms and of unknown duration.*

On Jan. 20, 1927, a farmer, aged 52, who had lived in Russia until the age of 16, came to the Mayo Clinic complaining of pain in the chest and general weakness. The family history was irrelevant. He had been married for twenty-six years and had nine children living and well. Appendectomy had been performed in 1915, and herniotomy in 1925. A moderate attack of influenza had occurred in 1918. He used coffee and tobacco in moderation. He had had a burning pain in the lower substernal region radiating through to the back for four

23. Glucose value "G" (Woodyatt) = 100 C + 0.58 P + 0.1 F.

years; this had been relieved by eating and drinking, and had not been aggravated by strenuous exertion. There had been periods of freedom from this pain for weeks at a time. He complained also of flatulence and periods of "sour stomach." Vision was poor. There was a slight chronic cough. For three years, exertion had provoked a little more dyspnea than normal. Moderate nocturia had been present for several years. He had been aware of an increase in the size of his face and hands for fifteen or twenty years.

The patient was obese, he was 5 feet 9 inches (175.3 cm.) in height, and weighed 213 pounds (97 Kg.). The features, hands and feet were typical of acromegaly. Sonorous râles were present at the hilum and the base of the right lung. The axillary lymph nodes were enlarged. The heart was normal except for distant sounds. The blood pressure was 120 systolic and 88 diastolic; the pulse rate was 104 and the temperature 99 F. There was bilateral recurrent inguinal hernia; spermatocele was found on the right. The prostate was moderately enlarged. The right palpebral fissure was larger than the left. Vision was about 6/15 in both eyes, and the visual fields were normal. The vocal cords were thickened and the arytenoids enlarged, suggesting acromegaly.

The specific gravity of the urine was 1.033, and its reaction acid; it contained a trace of albumin, 4.2 per cent sugar, or 51.08 Gm. in 1,200 cc. (twelve-hour specimen), but no acetone or diacetic acid; the microscopic examination was negative. The blood sugar was 240 mg. per cent. The hemoglobin was 87 per cent; the erythrocytes numbered 4,650,000 and leukocytes, 7,800. The Wassermann reaction was negative. The total gastric acidity was 42 and the free hydrochloric acid, 24. Fluoroscopy and roentgenography of the stomach gave negative results. A roentgenogram of the chest was negative except for moderate enlargement of the heart. The sella turcica was normal in size in the roentgenogram. An electrocardiogram showed a rate of 88, sinus rhythm, notched Q. R. S. complex in lead III and left ventricular preponderance.

The diagnosis was acromegaly and diabetes mellitus. The cause of the substernal pain was not determined.

The patient was given a diet containing 100 Gm. of carbohydrate, 42 Gm. of protein and 153 Gm. of fat (2,004 calories, 140 Gm. of glucose). Glycosuria was not present while this diet was maintained. The blood sugar on the third day was 180 mg. per cent.

CASE 3.—*Acromegaly with early diminution of glucose tolerance; clinical diabetes later, similar in all respects to ordinary diabetes; increased metabolism responding to rest; latent syphilis.*

On Oct. 15, 1921, a French-Canadian laborer, aged 51, presented himself for examination at the Mayo Clinic, complaining of rheumatic pains in the knees and hoarseness. The family history was irrelevant. He had been married thirty-five years and had one child, aged 21, living and well. The only event of importance in the history was a penile lesion at the age of 20, which had been cauterized. This had been followed by patchy alopecia. During the winter of 1919 and 1920, "rheumatism" of the left knee developed, and in June, 1921, the right knee became similarly affected. In January, 1921, he contracted a severe "cold" which lasted three months. A month after the onset of this cold he became hoarse. The hoarseness persisted but had been somewhat better during the month preceding admission. Aphonia had never been present. There had been some dyspnea during the last month and some obstruction to breathing at night. He had been perspiring excessively for the last two or three months. He had noticed that his hands had been getting larger for two or three months but did not think his feet had increased in size. No one had ever commented on a

change in his appearance, but he thought that his features had become altered, although he had never paid much attention to this. He thought that he had become more stooped.

The patient's skin was hairy; he was 5 feet 6 inches (167.6 cm.) tall and weighed 175 pounds (79 Kg.). The lower jaw and hands were large, the shoulders stooped and the chest barrel-shaped. He was bow-legged. All of the superficial lymph nodes were moderately enlarged, especially the cervical nodes. The knees creaked on passive motion. Moderate arteriosclerosis was present. The blood pressure was 182 systolic and 115 diastolic; the pulse rate was 94

Fig. 2 (case 3).—Lateral roentgenographic appearance of the basal region of the skull, showing the enlarged sella turcica.

and the temperature, 98.6 F. On the dorsum of the penis was a small scar. Laryngoscopy showed slight edema of the epiglottis and arytenoids with fixation of the left vocal cord in the bilateral abductor position; both vocal cords were reddened. This picture, other than the fixed cord, suggested acromegaly to the laryngoscopist. Vision in the left eye was 6/10 with correction, and in the right, 6/7 with correction. The visual fields were normal except that there was no color field for green or blue, with the 6/280 test object.

The urinalysis was negative. The Wassermann reaction was strongly positive twice. The spinal fluid was normal. The hemoglobin was 77 per cent; the erythrocytes numbered 4,360,000 and the leukocytes, 5,300. Two basal metabolic

tests were + 33 and + 21. A roentgenogram of the skull showed great enlargement of the sella turcica (fig. 2). Roentgenograms of the hands and feet were reported positive for acromegaly. A roentgenogram of the chest was negative. The result of a sugar tolerance test after the ingestion of 100 Gm. of glucose is recorded in table 1.

The patient was given two courses of six intravenous injections each of arsphenamine, and forty-two intramuscular injections of mercuric succinimide

On April 21, his condition was the same. He complained of sweating. The Wassermann reaction was positive.

On May 18, the Wassermann reaction was strongly positive.

On Jan. 6, 1926, the patient reappeared. He had not received any more antisyphilitic treatment. A year before this examination, polydypsia and polyuria developed, and a qualitative restrictive diet was given with injections of insulin three times a day for two weeks. The thirst and polyuria disappeared for six months and then recurred. He had not restricted his diet for the last few months. Since last seen, he had gained in weight for a time, but during the last year, in spite of a large appetite, he had lost 21 pounds (9.5 Kg.). At the time of examination he weighed 162 pounds (73.5 Kg.). He complained of slight

TABLE 1.—*Sugar Tolerance Test in Case 3*

Conditions of Test	Blood Sugar, Mg. per Cent	Glucose in Urine, per Cent	Amount of Urine, Cc.
Fasting	200	Trace	150
One-half hour after the ingestion of 100 Gm. glucose	230	Trace	30
One hour after ingestion of glucose	240	2.5	70
Two hours after ingestion of glucose	230	0.16	80
Three hours after ingestion of glucose	180	Trace	80

intolerance to heat, excessive perspiration and palpitation of the heart. He had been "weak in the knees" for the last five years. There had been loss of libido and potentia for one year. Vision had been somewhat blurred for three months. The additional observations in the physical examination at this time were a small adenoma in the right lobe of the thyroid and a right indirect inguinal hernia. The blood pressure was 136 systolic and 90 diastolic; the pulse rate was 110. There was moderate anemia of the secondary type, the hemoglobin being 68 per cent and the erythrocytes, 3,910,000; this was attributed to hemorrhoids. Vision was 6/20 in each eye, the reduction in acuity probably being due to opacities of the lens; the visual fields were normal. The Wassermann reaction was still strongly positive. Five infected teeth were demonstrated by the roentgen ray. The specific gravity of the urine was 1.041, and the urine contained 5.1 per cent sugar, or 109.1 Gm. in 2,140 cc. (twenty-four-hour specimen). The basal metabolic rate was + 32.

The metabolic rate and the diabetes were studied in preparation for inguinal herniotomy. The patient responded well to the prescribed diet and insulin. Under the influence of rest alone, the basal metabolic rate dropped from + 32 to + 5. The response to antidiabetic treatment became more satisfactory as the basal metabolic rate fell, but the decrease in the amount of urinary glucose was striking immediately after the institution of injections of insulin. Table 2 is a composite record of the diet, urine, estimation of blood sugar, insulin dosage and basal metabolic readings while the patient's metabolism was being studied, and table 3 is a record of the corresponding data while the diabetes was being studied.

CASE 4.—*Somewhat questionable acromegaly of unknown duration, with enlarged sella turcica but without signs of pressure; mild diabetes mellitus of unknown duration and without symptoms; tumor of the spinal cord with operation; necropsy.*

On Aug. 18, 1925, a Norwegian housewife, aged 68, first appeared at the Mayo Clinic complaining of pain in the left shoulder and numbness of the feet. The family history was irrelevant. She had been married twice, altogether for thirty-five years, and had had three children by her first husband; one of the children had died of tuberculosis and another had died in infancy. Catamenia had been normal, and menopause had occurred at the age of 49. She had not had any previous illnesses but had always been healthy and strong and a hard worker. Several months before examination, she began to notice that her feet felt cold and numb and that later they began to burn and ache. In going upstairs she would stub her toes and often fall. There was no sensation of pain when she struck her toes or bruised her shins. The numbness had increased in severity.

TABLE 2.—*First Series of Data Relative to Metabolism (Case 3)*

	Diet, Gm.				Urine						
Date, 1926	Carbohydrate	Protein	Fat	Glucose Equivalent*	Cubic Centimeters	Specific Gravity	Glucose, Gm.	Total Nitrogen, Gm.	Blood Sugar, Mg. per Cent	Insulin Units	Basal Metabolic Rate
1/ 8	199	61	208	255	2,210	1.042	79.22	14.14	334	..	+32
1/ 9	190	62	206	247	2,205	1.040	135.7	13.51	....	..	+25
1/10	196	65	209	255	2,785	1.033	145.6	13.27	....	..	....
1/11	170	63	210	228	2,625	1.025	119.0	11.42	....	..	+15
1/12	102	63	196	158	2,350	1.020	60.78	10.54	....	..	+16
1/13	100	58	205	154	1,840	1.014	20.41	9.94	364	50	+17
1/14	101	67	210	174	1,640	1.011	3.87	7.02	....	50	+15
1/15	99	58	197	152	1,535	1.015	6.41	8.06	250	50	+16
1/16	101	62	191	155	1,430	1.012	0.95	7.25	....	50	+ 8
1/17	101	66	212	160	955	1.019	1.31	6.05	....	50	....
1/18	101	66	208	160	1,545	1.020	1.92	8.48	....	50	+ 4
1/19	99	62	201	154	2,030	1.008	1.35	6.76	....	50	+ 7
1/20	101	62	209	157	1,705	1.015	1.57	....	....	50	— 1
1/21	102	62	209	158	.....	.....	....	....	....	50	+10
1/22	100	42	153	140	.....	.....	....	....	160	50	+ 5

* Glucose equivalent. G = 100 C. + 0.58 P. + 0.1 F. [Woodyatt: Arch. Int. Med. **28**: 125 (Aug.) 1921].

She became more and more unable to get about without help. In February she began to have "rheumatic" pains in the left shoulder, which radiated downward around the left side of the thorax to the sternum in front and to the interscapular region behind. The pain was a constant dull ache, which was worse at night. The movements of the arm were not limited. For the last four or five months she had been having trouble occasionally in controlling defecation, especially after the use of a cathartic; the desire to defecate would come suddenly and unannounced. Two months before examination, glycosuria was discovered and a diet was prescribed. Electric therapy had been carried out for the pain in the shoulder without relief. She had not noticed any change in her features or extremities; the onset of the condition had evidently been gradual for a number of years.

The patient was obese; she was 5 feet 4½ inches (163.8 cm.) tall and weighed 195 pounds (89 Kg.); her normal weight had been 220 pounds (100 Kg.). She had typical acromegalic features and hands and feet. The tonsils were chronically infected. The heart sounds were distant, the first apical sound muffled. Moderate arteriosclerosis and hypertrophic arthritis of the terminal joints of the fingers

were present. The left shoulder girdle showed muscular atrophy. Slight edema of the feet and legs was present. The left knee reflex was more active than the right. There was a positive Babinski sign and a suggestive Chaddock response on the left. The pupils were small and sluggish. Vision in the right eye was 6/7 with correction and in the left, 6/6 with correction. The fundi showed mild senile fibrosis. The visual fields were normal. There were a few peripheral lens opacities.

The first urine examined (twelve-hour specimen) contained 7.5 Gm. of sugar. The blood urea was 25 mg. per cent, the blood sugar 217 mg. per cent. The Wassermann reaction was negative. The hemoglobin was 77 per cent; the erythrocytes numbered 4,120,000 and the leukocytes, 5,600. A phenolsulphonphthalein test of renal function gave a return of 40 per cent of the dye in two

TABLE 3.—*Second Series of Data Relation to Metabolism (Case 3)*

Date,* 1926	Diet, Gm.				Blood Sugar Mg. per Cent	Insulin Units
	Carbohydrate	Protein	Fat	Glucose Equivalent		
1/24	100	60	208	156	...	..
1/25	100	60	208	156	...	..
1/26	100	60	208	156	...	..
1/27	100	60	208	156	...	..
1/28	100	60	208	156	...	..
1/29	100	60	208	156	...	..
1/30	100	60	208	156	...	..
1/31	100	60	208	156	...	..
2/ 1	100	60	208	156	...	..
2/ 2	100	60	208	156	...	..
2/ 3†	110	..	...	...	...	..
2/ 4	73	35	74	100	...	15
2/ 5	73	35	74	100	...	15
2/ 6	73	35	74	100	...	15
2/ 7	100	42	153	140	...	15
2/ 8	100	42	153	100	...	15
2/ 9	54	45	206	100	...	15
2/10	54	45	206	100	...	15
2/11	54	45	206	100	130	15
2/12	54	45	206	100	...	15
2/13	54	45	206	100	...	15
2/14	54	45	206	100	...	15
2/15	54	45	206	100	...	15
2/16	54	45	206	100	...	15
2/17	54	45	206	100	147	15
2/18	54	45	206	100	...	15

* Glycosuria was not present during this period.
† Herniotomy.

hours (intravenous administration). A roentgenogram of the skull showed moderate enlargement of the sella turcica (fig. 3). One of the chest revealed an upper mediastinal shadow, which was diagnosed as a small substernal goiter.

The patient was kept in the hospital for ten days on a diet containing 100 Gm. of carbohydrate, 42 Gm. of protein and 153 Gm. of fat (calories, 2,002, 140 Gm. of glucose). The urine remained practically sugar-free on this diet, except for an occasional faint trace. The patient was sent home on a qualitatively restricted diet. The diagnosis was acromegaly, mild diabetes mellitus of the vascular type and suspected tumor of the spinal cord.

On Jan. 15, 1927, the pain in the left shoulder and thorax had become more severe and was aggravated by stooping or lifting but not by straining. Weakness of the legs had become more marked, and spasticity had developed; for two months the patient had been completely paralyzed from the waist down and had been confined to bed. During this time muscular atrophy of the legs had developed. The numbness had extended up the legs to a level just above the

umbilicus, and there was almost complete anesthesia in this area to pain and temperature with some reduction of tactile sensation. For the previous month there had been frequent painful flexor spasms of both legs, which would often wake the patient at night. Control of the rectal sphincter had been practically lost, and control of the bladder had become affected later.

The patient weighed 35 pounds (17 Kg.) less than on the previous examination. There was practically complete loss of power of the abdominal muscles and of both lower extremities, with spasticity, partial clonus, increased reflexes and definite anesthesia up to the level of the sixth dorsal segment. Tenderness was

Fig. 3 (case 4).—Lateral roentgenogram of the basal region of the skull, showing the enlarged sella turcica.

present over the fifth dorsal vertebra. The visual fields were normal. The thyroid was not palpable, although the roentgenogram showed a substernal goiter. The blood pressure was 140 systolic and 88 diastolic, and the pulse rate was 106.

The specific gravity of the urine was 1.031 and the reaction acid; the urine contained a trace of albumin, and 1.1 per cent, or 4.8 Gm. of sugar in 400 cc. The blood urea was 24 mg. and the blood sugar, 260 mg. per cent. The hemoglobin was 78 per cent; the erythrocytes numbered 4,420,000 and the leukocytes, 4,200. The spinal fluid was slightly yellow, was positive for globulin, contained one lymphocyte to the field, and gave a pressure of 2.0 cm.; there was no

response to jugular pressure. The benzoin sol curve was 0000033333332000. A roentgenogram of the spine showed hypertrophic arthritis of the cervical, dorsal and lumbar regions.

A tumor of the spinal cord at the level of the fifth or sixth dorsal vertebra was diagnosed and laminectomy decided on. The patient was admitted to the hospital and given a qualitative restriction diet. At the end of five days the blood sugar was 120 mg. per cent; there was a trace of sugar in the urine on only two occasions.

On January 26, the patient was taken to the operating room but collapsed following procaine hydrochloride anesthesia, and was sent back to her room. She quickly recovered from this condition.

On January 28, there was 2.1 per cent (19.53 Gm) of sugar in the urine; on January 29, 0.92 per cent (6.58 Gm.) and on January 31, only a trace. On

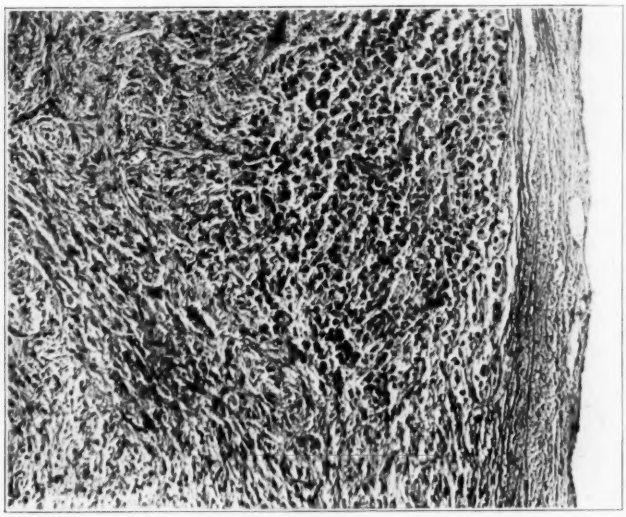


Fig. 4 (case 4).—Small adenoma in anterior lobe of the pituitary gland; ×60.

the same day, under ethylene and ether anesthesia, laminectomy of the fourth, fifth and sixth vertebrae was performed. Directly beneath the fifth a hard, fixed tumor was found; the dura was opened and a calcified endothelioma, measuring 1.0 by 1.8 cm. was exposed; it lay posteriorly and to the left and flattened the cord to a mere ribbon. The tumor was removed and the dura closed. The patient's condition was good throughout the operation, and the blood pressure was 120 systolic at the end. She regained consciousness but suddenly died later the same day.

The essentials of the pathologic report by J. W. Kernohan are as follows: The pituitary gland was about twice the normal size. It contained large collections of colloid material. The pars intermedia showed glial proliferation. The pars anterior was larger than normal, and throughout its entirety some acini were seen which contained small collections of colloid and stained pale with

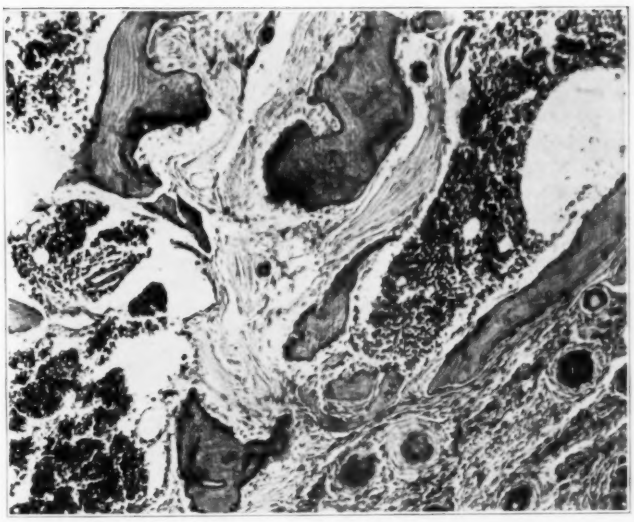


Fig. 5 (case 4).—Section through the ossified endothelioma of the spinal cord; × 60.

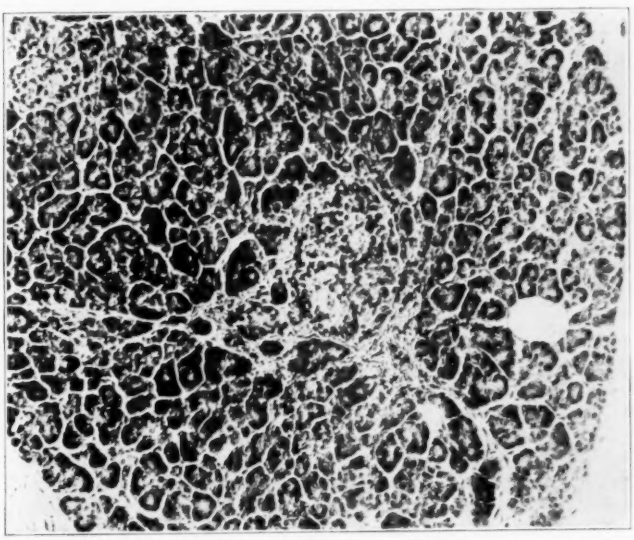


Fig. 6 (case 4).—Section through the tail of the pancreas, showing fibrosis and hyalinization of one of the islands of Langerhans; × 120.

hematoxylin. The majority of the cells were eosinophilic but some were basophilic in reaction. There was a small adenoma just beneath the capsule of the pars anterior, composed mainly of eosinophilic cells (fig. 4). There were also several small adenomas in the substance of the pars anterior similar to this. An occasional mitotic figure was seen throughout the pars anterior.

The tumor of the spinal cord was a typical endothelioma, with numerous psammoma bodies and some large areas of ossification with bone marrow spaces containing fat and blood cells (fig. 5).

In the head of the pancreas was a considerable degree of replacement of fat. The islands of Langerhans were, for the most part, of normal appearance. A few showed slight excess of fibrous tissue. In the body of the pancreas considerable arteriosclerosis was noted throughout, but the islands did not show

Fig. 7 (case 5).—Appearance of patient thirteen years previous to the first examination.

notable changes. In the tail of the gland the majority of the islands appeared normal, but a few showed fibrosis and hyalinization (fig 6). Excessive fat was observed in sections of the liver stained with scharlach R.

CASE 5.—*Acromegaly of thirteen years' duration with beginning signs of pressure; history of symptoms of hyperthyroidism for five years; diabetes mellitus somewhat atypical, of two years' duration, with two attacks of coma; thyroidectomy and death.*

On June 1, 1927, a woman, aged 41, presented herself for examination at the Mayo Clinic with the complaint of diabetes. The family history was irrelevant. She had been married twenty years without the desired pregnancy. Menstruation had begun at the age of 13 and had been regular until twelve years before admission, when menopause suddenly occurred at the age of 29, although there was a slight flow once in 1920. She had not been ill except for a mild attack of influenza in 1916. She had been examined previously at the Mayo Clinic in December, 1920. Her complaint then had been puffiness and enlargement of the

acral parts and the face, of six or seven years duration. At first there had been considerable aching in the forearms and hands. She had had to wear gloves and shoes two sizes larger than usual and had gained 20 pounds (9.9 Kg.). She felt well except that all work was an effort. For two years there had been a large goitrous swelling in the right side of the neck, but after administration of thyroid extract for fifteen months the size of this was greatly reduced. The skin had previously been dry but had become moist and less puffy. Her appearance was strikingly different from what it had been thirteen years before, as shown by a photograph taken at that time (fig. 7). On examination at that time, typical acromegaly was found. The sella turcica was enlarged (graded 4) and the posterior clinoid processes eroded. The visual fields were normal. Glycosuria was not present. Estimation of the blood sugar was not made. Two basal metabolic

Fig. 8 (case 5).—*A*, front view of patient as she appeared at the time of the last examination, showing typical acromegalic physiognomy and acromegalic appearance of hands. *B*, side view of same patient.

rates were +7 and +4. The thyroid gland was not reported as being enlarged. The patient was discharged without medication.

About two years later, symptoms suggestive of hyperthryoidism appeared: nervousness, tremor, intolerance to heat, undue perspiration, excessive appetite and easily induced fatigue. However, there was no loss of weight. These symptoms had persisted for three years when polydipsia and polyuria appeared; the patient then began to lose weight, but the symptoms of hyperthyroidism were greatly ameliorated and she felt better and stronger. Six months after the onset of thirst and polyuria, she suddenly became comatose. Her physician diagnosed the condition as diabetic coma, administered insulin, and after two days she regained consciousness. From then on, she was on a weighed diet containing 50 Gm. of carbohydrate, 60 Gm. of protein and 130 Gm. of fat (98 Gm. of glucose); she took ten units of insulin three times a day. The thirst and polyuria

soon disappeared; she felt well, and the puffiness of the features and extremities decreased markedly, so that she was able to wear shoes a size smaller. She gradually lost 29 pounds (10.3 Kg.) in weight. During the year and a half on this regimen, the urine was tested frequently but sugar was never found. (However, the Benedict's solution she used was afterward found to be worthless.) During this time she did not have more than four or five recognizable reactions to insulin.

About a week previous to examination, June 1, 1927, the patient became nauseated and lapsed into somnolence. The attending physician found large amounts of glucose in the urine, whereupon he administered 300 units of insulin within forty-eight hours. At the end of this time, the patient awoke for half

Fig. 9 (case 5).—Lateral roentgenographic appearance of the skull, showing the enlarged sella turcica and the "putty finger" markings of increased intracranial pressure.

a day but relapsed into coma. A consultant was called from the Mayo Clinic, and he decided that she had been revived from impending diabetic coma only to go into a state of hypoglycemic shock. He administered 20 Gm. of glucose intravenously, and she recovered. The patient resumed her former diet, but took fifteen units of insulin instead of ten units three times a day. During five days with this dosage there was only one insulin reaction and the urine was sugar free.

At this time the appearance of the patient was about as it had been seven years before; large nose, prognathism, puffy eyelids, large fissured tongue, widely separated teeth, large spade-like hands and feet and genu varum (fig. 8). The skin, however, was only slightly thicker than normal. She was 5 feet 2 inches

(157.5 cm.) tall and weighed 133 pounds (61 Kg.). The thyroid gland was enlarged, the right lobe measuring about 3.5 by 6 cm. and the left about 2.5 by 5 cm.; definite nodules were not palpable, and bruits were not audible. There was slight tremor of the fingers but no weakness of the quadriceps muscles. The heart was slightly enlarged to the left, with a faint systolic murmur over the precordia. There were several rows of flat brownish verrucae about the torso below the costal margin. The finger nails were small and triangular, with longitudinal striations and absence of the crescents. The uterus was small and atrophic. The blood pressure was 104 systolic and 68 diastolic, the pulse rate 80 and the temperature 99 F. Vision in the right eye was 6/12 with correction and in the left, 6/60 with correction. The left temporal field was slightly contracted, and the left optic disk somewhat pale.

The first urine examined did not contain sugar and had a specific gravity of 1.006 (the patient was on a diet and was taking insulin). The blood sugar was

Fig 10 (case 5).—Bony overgrowth of the phalanges and tufting of the distal ends of the terminal phalanges.

173, blood urea 10 mg. per cent and the carbon dioxide combining-power, 63 volumes per cent. The hemoglobin was 87 per cent; the erythrocytes numbered 4,660,000 and the leukocytes 4,500. The Wassermann reaction was negative. A roentgenogram of the skull showed that the sella turcica was about as before, but that there was now also evidence of marked increased intracranial pressure (fig. 9). Roentgenograms of the teeth showed periapical infection in all of the lower and in five of the upper teeth. Roentgenograms of the hands revealed overgrowth of bone of the phalanges and typical acromegalic tufting of the distal ends of the terminal phalanges (fig. 10).

Table 4 shows the daily estimations of sugar, and nitrogen in the urine, blood sugar, insulin dosage, basal metabolic records and dosage of compound solution of iodine (Lugol's solution) for the period of three and a half weeks in the hospital. During this time, the patient was getting a weighed diet containing 77 Gm. of carbohydrate, 50 Gm. of protein and 140 Gm. of fat (1,768 calories, 120 Gm. of glucose).

On June 10, the estimations of blood sugar and urinalyses were made after a period of fasting and at intervals of half an hour up to noon after a breakfast containing approximately 40 Gm. of available glucose. The results are recorded in table 5. These figures show merely that the renal threshold for glucose was at least not lower than 0.155 mg. of glucose for each hundred cubic centimeters of blood.

Six estimations of the respiratory quotient during the first two weeks were 0.82, 0.83, 0.81, 0.81, and 0.82, showing theoretically, at least, utilization of glucose.

Three basal metabolic rates before administration of iodine were + 31, + 27, and + 32, and on the seventh, eighth, tenth, seventeenth and nineteenth days of administration of 30 minims (1.9 cc.) of compound solution of iodine daily in three doses of 10 minims (0.6 cc.) each, + 26, + 20, + 21, + 19 and + 20.

TABLE 4.—*Data Relative to Metabolism and Treatment (Case 5)**

Date, 1927	Urine Glucose, Gm.	Urinary Nitrogen, Gm.	Fasting Blood Sugar, Mg. per Cent	Insulin Units	Compound Solution of Iodine (Lugol's Solution) Minims	Basal Metabolic Rate
6/ 1	....	....	173	10-10-10	..	+31
6/ 2	Trace	....	...	10- 0-10	..	....
6/ 3	11.9	....	...	None	..	+27
6/ 4 †	....	....	...	None	..	....
6/ 5	Trace	....	...	0- 0-10	..	....
6/ 6	....	....	...	10- 0-10	20	....
6/ 7	....	....	...	10- 0-10	30	+32
6/ 8	....	....	146	10- 0-10	30	....
6/ 9	15.9 (?)	....	...	10- 0-10	30	....
6/10	....	....	...	None	30	....
6/11 †	....	....	155	None	30	....
6/12	....	5.89	...	None	30	+26
6/13	....	4.05	135	None	30	+20
6/14	....	1.56	137	None	30	....
6/15	3.35	4.1	160	None	30	+21
6/16	....	3.54	165	None	30	....
6/17	....	1.7	167	None	30	....
6/18	....	....	155	None	30	....
6/19	....	....	...	None	30	....
6/20	....	1.12	142	None	30	....
6/21	Trace	3.07	144	None	30	....
6/22	....	1.4	...	None	30	+19
6/23	Trace	6.56	...	None	30	....
6/24	....	....	144	.....	30	+20

* During the period in which these records were made, the diet contained 77 Gm. of carbohydrate, 50 Gm. of protein and 140 Gm. fat (1,768 calories, available glucose, 120 Gm.)
† Sunday, tests not made.

H. S. Plummer diagnosed the condition as hyperfunctioning adenomatous goiter, and advised thyroidectomy. It was decided, however, to treat the pituitary gland with roentgen rays first to determine whether the basal metabolic rate could be lowered by this means and thus to determine whether there was a relationship between the pituitary condition and the increased metabolism. Accordingly, three treatments were given and the patient dismissed with instruction to take 10 minims of compound solution of iodine daily and to return for reexamination in six weeks.

During this period at home, the patient adhered strictly to the weighed diet. She examined the urine daily for sugar and found it normal except on a few occasions when the reaction indicated slight reduction; at such times, she took 5 units of insulin. Subjectively, she was much better.

On Aug. 5, 1927, she returned to the clinic. The first twenty-four-hour specimen of urine produced complete reduction, but the following day only a

trace of sugar was present. The blood sugar was 325 mg. per cent. Two basal metabolic rates were + 36 and + 47.

Partial thyroidectomy was performed (Pemberton) on August 13. The right lobe was enlarged to about four times the normal size. Three fourths of this lobe was removed, but the left lobe, being normal in size, was not removed. The pathologist reported multiple, small, hemorrhagic, fibrous, calcareous, degenerating colloid and fetal adenomas in a colloid thyroid.

Immediately after operation, the pulse rate jumped to 138 and gradually increased to 178 at the time of death nine days later. There was moderate elevation of temperature, which subsided on the fourth day and then gradually climbed to 105.5 at the time of death. The patient perspired profusely and became more and more restless. She slept a great deal but could easily be aroused. During the last two days before death, she was semidelirious. Administration of iodine was discontinued after operation for three days and then resumed, 30 minims of compound solution of iodine being given daily. Table 6 shows the daily amount of sugar in the urine, the presence or absence of diacetic acid and acetone in the urine, blood sugar, carbon dioxide combining-power of the blood, insulin dosage and amount of glucose and sodium bicarbonate administered from the second day before operation until death. Necropsy was refused.

TABLE 5.—*Repeated Estimation of Sugar in Blood and Urine (Case 5)*

Time	Blood Sugar, Mg.	Urine,* Cc.
8:00 a. m.	0.148	10
Breakfast, 8:15 to 8:30		
9:00	0.140	300
9:30	0.129	275
10:00	0.155	75
10:30	Blood clotted	50
11:00	0.149	75
11:30	0.142	25
Noon	0.142	175

* Sugar was not found in the urine at any time.

CASE 6.—*Acromegaly of many years' standing without signs of pressure; diabetes mellitus of seven years' duration; increased metabolism; adenomatous thyroid gland.*

On Aug. 22, 1927, a steel worker, aged 44, came to the Mayo Clinic because of diabetes mellitus. The family history and early personal history were unimportant. Seven years previously, weakness, polyuria, polydipsia and polyphagia had appeared. The condition was diagnosed as diabetes mellitus and the diet loosely restricted qualitatively in carbohydrates. A year later he began to take insulin and during the last two years had often taken as much as 160 units in a day without severe reaction. Five or six years before admission, the patient complained of nervousness and palpitation. Three years before admission, headaches began and became almost constant; they were mainly frontal and temporal. Attacks of dizziness recurred at irregular intervals and sometimes caused the patient to fall to the ground but without loss of consciousness. Diplopia was present on several occasions, and a slight degree of photophobia persisted. Thickness of speech had been present for two years. Two years previously, all of the teeth had been extracted and following this the patient complained of weakness of the left side which gradually disappeared in the course of three months. This had been attributed to cerebral embolism. Sexual desire was completely lost. For two years he had been unable to work because of weakness.

The patient stated that he had not noticed any alteration in his features, but his brother asserted that they had become coarse in the last few years. From comparison with an old photograph, it was evident that the features had actually undergone a distinct change during the last twenty years. The patient recalled that he had been wearing a larger hat during the last ten years.

The patient was 5 feet 6 inches (167.6 cm.) tall and weighed 180 pounds (82 Kg.). The features were typical of acromegaly, the skin coarse, and the hands and feet large. A small adenoma, less than 1.0 cm. in diameter, was palpable in the right lobe of the thyroid gland. A moderate degree of weakness of the quadriceps, slight tremor of the fingers and some undue sweating were present. The tonsils were moderately enlarged and contained soft plugs. The teeth were artificial. Vision was normal, and the visual fields and ocular fundi did not show any significant changes. The blood pressure was 148 systolic and 90 diastolic; the pulse rate ranged constantly around 100, and the temperature was 98 F.

TABLE 6.—*Laboratory and Therapeutic Data Before and After Thyroidectomy (Case 5)*

Date, 1927	Amount of Urinary Glucose, Gm.	Urinary Diacetic Acid	Urinary Acetone	Blood Sugar, Mg. per Cent	Carbon Dioxide Combining Power, per Cent by Volume	Insulin Units	Glucose Equivalent With Diet, Gm.	Sodium Bicarbonate Intravenously, Gm.
8/11	10.4	..	..	...	..	...	140	..
8/12	....	..	..	...	..	...	120	..
8/13*	13.5	..	+	392	..	20	50	..
8/14	49.7	..	+	...	..	30	75	..
8/15	87.0	+	+	350	..	30	120	..
8/16	84.3	+	+	400	29	90	118	45
8/17	124.6	+	+	400	38 (8 a.m.) 37 (2 p.m.)	80	133	..
8/18	58.9	+	+	426	30	135	127	25
8/19	64.5	+	+	454 (8 a.m.) 454 (2 p.m.) 454 (4 p.m.)	30	215	120	..
8/20	27.3	..	..	500	51	160	120	..
8/21	....	..	..	...	..	20	25	25

* Thyroidectomy.

The urine had a specific gravity of 1.032 and contained a moderate amount of albumin and sugar. The blood sugar was 206 mg. per cent. The Wassermann reaction was negative. The hemoglobin was 74 per cent; the erythrocytes numbered 4,260,000 and the leukocytes, 10,900. A roentgenogram of the chest revealed a small substernal goiter, and one of the skull showed enlargement of the sella turcica with thinning of the posterior clinoid processes. Two basal metabolic rates taken before the administration of iodine were +28 and +27, and after the patient was given compound solution of iodine (30 minims daily for seven days) the rate was +30.

The patient was kept in the hospital for two weeks on a diet containing 65 Gm. of carbohydrate, 50 Gm. of protein and 260 Gm. of fat (2,790 calories, 120 Gm. of glucose). Traces of sugar appeared in the urine on this diet, and 10 units of insulin twice daily was required to keep the urine sugar free. On the diet alone the blood sugar dropped to 165 mg. per cent. The patient's condition improved considerably under treatment. Thyroidectomy was considered, but the patient decided to wait for a while before operation.

COMMENT

The six cases reported demonstrate the similarity of "acromegalic diabetes" to ordinary diabetes mellitus. Polyuria and polydipsia were present in the more severe forms of diabetes and were proportionate to the intensity of the disease. Cases 1 and 3 illustrate the point made previously that the incidence of the association of diabetes and acromegaly may be greatly underestimated. In case 1, the diabetes was mild and readily controlled by diet. If this patient had been examined at a time when she was eating sparingly of food containing carbohydrate the glycosuria would not have been discovered and the diabetes would have passed unrecognized in the absence of an estimation of blood sugar, as there was evidently a high renal threshold for glucose. In case 3, the urine was free from sugar three years before the clinical appearance of diabetes, but the fasting blood sugar was 200 mg. per cent and a diabetic glucose tolerance curve was obtained at that time.

Three of the cases were readily controlled by diet alone, and the other 3 required insulin as well. The response to insulin was just as striking as in any case of diabetes. From table 2, it is apparent that in case 3 the response to antidiabetic treatment became more satisfactory as the basal metabolic rate fell to normal under the influence of rest. Wilder emphasized the influence of hyperthyroidism with its increased metabolism on the severity of diabetes. This observation, however, does not detract from the validity of the effect of insulin in this case, since there was an immediate and marked decrease in the urinary glucose after the administration of insulin. In case 5 (table 4), it was possible to keep the diabetes under control without insulin after the basal metabolic rate began to fall under the influence of iodine. That improved tolerance results from the administration of iodine to persons with combined exophthalmic goiter and diabetes has been shown by Boothby [24] and Wilder.

Apparently, there have been few patients with "acromegalic diabetes" who have been carefully treated with insulin. Colwell [5] recently reported a patient who had acromegaly with diabetes who responded to insulin in a manner similar to that observed in ordinary diabetes. Blum and Schwab [25] compared the blood-sugar curves after the administration of 30 units of insulin in a case of diabetes unassociated with acromegaly and in one associated with that disease and observed

24. Boothby, W. M., and Wilder, R. M.: Metabolism Studies in Exophthalmic Goiter Complicated by Diabetes, J. Clin. Investigation **1**:590, 1924-1925. Wilder, R. M.: Hyperthyroidism, Myxedema and Diabetes, Arch. Int. Med. **38**: 736 (Dec.) 1926.

25. Blum, L., and Schwab, H.: Diabète acromégalique et insuline, Compt. rend. Soc. de biol. **89**:195, 1923.

a similar reduction curve in both. After the administration of insulin, one of John's patients responded as expected, but a weighed diet was given at the same time so that the exact effect of the insulin is not certain. This case was extremely interesting, as the blood sugar and glucose tolerance were normal three months later, although the diet during that time had been liberal. In a recent article, Davidoff and Cushing [20] concluded that "insulin will control acromegalic diabetes but far less effectively than it does the more common forms of diabetes unassociated with hyperpituitarism, the assumption being that the increased pituitary activity tends to counteract its effects," but they did not bring out striking or convincing evidence on this point, describing only a case in which the blood sugar apparently was not much affected by insulin until after a "generous portion of his pituitary adenoma was removed." Furthermore, they had previously remarked, "three of our patients with acromegalic disease . . . . had been shown to respond normally to insulin . . . ." So far, the balance of evidence at hand from a clinical standpoint certainly favors the deduction that insulin acts in "acromegalic diabetes" just as it does in diabetes without acromegaly.

While it is not my object in this paper to discuss particularly the question of the rate of metabolism in acromegaly or the much debated question of the possible interrelationship between the pituitary and thyroid glands, a few words in this regard would not be amiss, since 3 of these patients (cases 3, 5 and 6) presented the interesting combination of acromegaly, diabetes mellitus and increased metabolism.

In case 3, there was an elevation of the basal metabolic rate which gradually dropped to normal during a rest period of two weeks. There was a palpable adenoma of the thyroid gland, and some symptoms suggested hyperthyroidism. The history indicated that the diabetes was greatly aggravated about the time that the latter symptoms became manifest. However, "the recognition of mild grades of hyperthyroidism is often a difficult matter, and in the presence of diabetes it becomes doubly difficult owing to the fact that certain symptoms, notably bulimia, loss of weight and weakness, are common in both conditions" (Wilder).

The history in case 5 suggests that the onset of hyperthyroidism took place five years before the second examination at the Mayo Clinic and that the diabetes began three years after the onset of the hyperthyroidism. The patient may have been on the crest of a wave of hyperthyroidism at the time of the first attack of coma and again later with the attack of impending coma. This possibility, however, is not clearly ascertainable from the history. It is also difficult to explain the improvement in the symptoms of hyperthyroidism with the onset of the diabetes, a point on which the patient insisted. Likewise, the definite improvement in the acromegaly after the onset of the diabetes

is inexplicable. If it had occurred with the onset of the symptoms of hyperthyroidism, it could have been due to the disappearance of previous myxedema complicating the acromegaly. The reason for this patient's death after partial thyroidectomy is difficult to explain. The picture did not resemble any other known condition. There was not sufficient acidosis to cause death; in fact, it was under control the preceding day.

Thyroid crisis would explain the inability of insulin to affect the blood sugar, but thyroid crisis is incompatible with the histologic picture of the gland. The cause of death in this case will probably always remain a mystery. In general, acromegaly is regarded, without any definite reason, as increasing the surgical risk.

In case 6 there is a likelihood that the diabetes was precipitated or at least aggravated by the onset of hyperthyroidism, although the time relations are not very clear. In this case there were many mild symptoms of hyperthyroidism, and a small adenoma was palpable in the gland.

In 1897, Magnus-Levy [26] called attention to such symptoms as cardiac hypertrophy, exophthalmos, tachycardia and sweats in patients with acromegaly. The experiments of Crowe, Cushing and Homans [27] in 1910 showed that adiposity, lethargy and subnormal temperature followed hypophysectomy in young animals. In 1927, Cushing and Davidoff [28] reported that in 45.8 per cent of 72 cases of acromegaly the basal metabolic rate was above + 10 and also that in 25 of 100 cases of acromegaly the thyroid was palpable or definitely enlarged; in 17 of these reliable studies of the basal metabolic rate were made, and in 15 it was found to be elevated. However, in 75 per cent of the cases in which the rate was definitely elevated, the thyroid gland was not even palpable. In contrast with these observations, the basal metabolic rate in 58 proved cases of hypopituitarism was below — 10. Thyroidectomy in some of their cases served to lower the basal metabolic rate and iodine was shown also to lower it, although the gland in the three cases in which operation was performed showed merely colloid changes of adenomatous type "without expected evidence of toxicity." On the other hand, operations on chromophilic adenoma of the pituitary gland with elevated basal metabolic rate not associated with palpable enlargement of the thyroid were followed by a uniform and striking fall in the basal metabolic rate. Cushing and Davidoff [28] concluded

26. Magnus-Levy, A.: Untersuchungen zur Schildrüsenfrage, Ztschr. f. klin. Med. **33**:269, 1897.

27. Crowe, S. J.; Cushing, Harvey, and Homans, John: Experimental Hypophysectomy, Bull. Johns Hopkins Hosp. **21**:127, 1910.

28. Cushing, Harvey, and Davidoff, L. M.: Studies in Acromegaly: IV. The Basal Metabolism, Arch. Int. Med. **39**:673 (May) 1927.

that the chromophilic cells of the anterior lobe of the pituitary gland secrete a substance which not only contains the hormone of growth but which is capable of raising the basal metabolic rate, and that whether it acts as a stimulus to metabolism directly on the tissues or only through intermediation of the thyroid gland cannot as yet be definitely stated.

Of the 79 cases of acromegaly in the series from the Mayo Clinic, the thyroid gland was definitely abnormal by palpation in 34 (43 per cent). The basal metabolic rate was determined in 57 of the 79 cases. Of these 57, there were 29 in which the basal metabolic rate was above + 10; however, in 13 of these the examination was made in the earlier days, and only one rate was determined. In 3 cases not showing evidence of goiter or hyperthyroidism, the rate was elevated; in one of these, seven determinations varied between + 53 and + 30. In none of the 57 in which the rate was estimated was it below — 10, and in only 4 was it between zero and — 10. It is definitely established, therefore, that both abnormal thyroid glands and increased metabolism are common in cases of acromegaly. What relation there is between the two glands is difficult to decide on the present data.

Case 4, while not a cleancut example of acromegaly, was sufficiently suggestive and interesting to be included in this report. The tumor of the spinal cord was extremely interesting; it was a typical endothelioma, but the large areas of ossification with bone marrow are unusual. If one should consider this a case of acromegaly, it would afford interesting speculation to associate the growth of bone tissue in the tumor with hyperactivity of the pituitary gland. The observation at necropsy of the degenerative changes in the islands of Langerhans, found mainly in the tail of the pancreas, while interesting, do not throw any light on the relationship of the diabetes to the pituitary hyperplasia. Few references have been made to changes in the islands of Langerhans in "acromegalic diabetes." Some of the early necropsy reports mention pancreatic lesions, but they usually consisted of interlobar fibrosis, the islands being apparently normal. A few references have been made, however, to the occurrence of significant microscopic changes in the islands; some writers have cited instances of atrophy, hyperplasia, fatty degeneration, hyalinization or sclerosis of the islands, but many of these were in cases of acromegaly without diabetes. Norris [29] described adenomatous hypertrophy of the pancreatic islets in a case of acromegaly with diabetes. Kraus [30] reported sclerosis of the islands

29. Norris, C.: A Case of Acromegalia, Proc. New York Path. Soc. **7:** 19, 1907-1908.

30. Kraus, E. J.: Die Beziehungen der Zellen des Vorderlappens der menschlichen Hypophyse zueinander unter normalen Verhältnissen und in Tumoren, Beitr. z. path. Anat. u. z. allg. Path. **58:**159, 1914.

in another case. Cushing and Davidoff [31] reported on the condition of the islets in two cases of acromegaly and diabetes: in one, in which the glycosuria had disappeared, there was an increase in the number and hypertrophy of the islets; in the other, after death in diabetic coma, the islets were normal (except for a single island which was slightly sclerosed). The frequent absence of demonstrable changes in the islands in cases of diabetes unassociated with acromegaly is well known. The accepted theory of diabetes as a disorder of the islands of Langerhans has found meager substantiation from the anatomic standpoint.

SUMMARY

A brief summary of the results of the main experimental and clinical investigations on the question of the relationship of the pituitary gland to carbohydrate metabolism has been given. Six more cases have been recorded of the interesting combination of acromegaly and diabetes mellitus, in 3 of which insulin was required. In 1 of these cases, the diagnosis of acromegaly is admittedly questionable. Four others of a series of 79 cases of acromegaly showed some disturbance of carbohydrate metabolism, but this feature was not carefully studied in them. The diabetes in the 6 cases reported was in all essential respects similar to the ordinary form and responded similarly to diet and insulin therapy. Three of the patients presented the unique complication of increased basal metabolic rate, in all three of whom it was presumably due to hyperthyroidism.

CONCLUSIONS

1. The assumption that the diabetes associated with acromegaly is due to the same cause which produces the acromegaly derives its main support from the following points: (1) Acromegaly (hyperpituitarism due to chromophilic hypophyseal adenoma) is frequently associated with diabetes mellitus; (2) The syndrome of hypopituitarism (due to chromophobe hypophyseal adenoma) is infrequently associated with diabetes mellitus; (3) even though hypophysectomy in man has never been followed by a cure of the diabetic condition, it has been followed by a state of increased sugar tolerance, as shown in a few instances by the intravenous tolerance test; this increase in tolerance has been demonstrated even when clinical diabetes did not exist; (4) even though clinical diabetes may not be present, glucose tolerance may be diminished in cases of acromegaly, as shown in a few instances by the intravenous tolerance test; (5) transient hyperglycemia and glycosuria may be produced by the injection of pituitary extracts, and (6) pituitary

31. Cushing and Davidoff (footnote 1, second reference).

extract is capable of preventing or relieving hypoglycemia and convulsions produced by injection of insulin.

2. The only difference between diabetes alone and diabetes associated with acromegaly is its occasional spontaneous temporary or permanent disappearance, a point which has been demonstrated in relatively few cases.

3. It would seem to be most plausible, then, to assume that the diabetes occurring with acromegaly is due to the same factor producing ordinary diabetes, namely, an insufficient production of insulin, although it is possible that enough insulin might be secreted but might be neutralized by some new substance.

4. The relation of the hypophysis to carbohydrate metabolism is still far from settled, but there is no doubt of the existence of a relationship.

STOMACH TONUS AND PERIPHERAL LEUKOCYTE COUNT (SPLANCHNOPERIPHERAL BALANCE) *

SERGIUS ARQUIN, M.D.
CHICAGO

For a long time it has been known that there is a definite correlation between the peripheral leukocyte count and the various phases of digestion. During recent years, this subject has been investigated with greater interest in relation to functional pathology of the liver (Widal's hemoclastic crisis).

In a series of leukocyte counts on eighty normal persons, Feinblatt [1] has shown conclusively that following the ingestion of even a small quantity of food a distinct increase in the peripheral leukocyte count resulted within from one to one and one-half hours. Bien and Variekamp,[2] taking counts at more frequent intervals, have shown the details of this postprandial curve. Immediately after ingestion there is a fall in the count; within from ten to twenty minutes, this is followed by a slight rise back to normal or slightly above it. For the next thirty to fifty minutes, the leukocyte count is low—below the starting point—and after this period of depression, it rises in the true digestive leukocytosis.

Numerous observers have found that children show a more marked leukopenia than adults, and in those cases which are followed by alimentary leukocytosis (which is not constant in children), the count shows a greater percentage of increase than is true in adults.[3]

The question of the relation of the type of food ingested to the leukocyte count has also been worked out, chiefly in relation to the hemoclastic crisis. Although some observers report a difference with the types of food,[4] the majority feel that the variations in both quantity and quality of the material ingested show little if any effect on the number of white cells in the peripheral blood.

In pathologic conditions, especially in relation to disorders of the liver, as Widal first pointed out, there appears to be some disturbance

---

* From the Department of Pathology of the College of Medicine, University of Illinois, Laboratory of Dr. W. F. Petersen.

1. Feinblatt, H. M.: Alimentary Leukocytosis in Eighty Normal Men, J. A. M. A. **80**:613 (March 3) 1923.

2. Bien, S., and Variekamp, H.: J. Exper. Med. **36**:415, 1924.

3. Glaser, F.: Med. Klin. **18**:331, 1922. Abel, E., and Brenas, P.: Compt. rend. Soc. de biol. **86**:1040, 1922. Mautner, H., and Cori, G.: Klin. Wchnschr. **1**:523, 1922. Misasi, M., and Aiello, G.: Pediatric, Naples, **30**:408, 1922. Muriac, P.: J. de méd. de Bordeaux **92**:375, 1921. Schippers, J., and de Lange, C.: Nederl. Tijdschr. v. Geneesk. **66**:894, 1922.

4. Brodan, P., and Sangerons, F.: Presse méd. **26**:124, 1918.

of the regulatory balance. The conviction has grown, however, that this is by no means a peculiarity of hepatic disorders.[5]

The explanations for the leukocytosis following ingestion of food are manifold. Goodall and Paton [6] believe that the phenomenon results from an increased function of the bone marrow, with an actual increase in the number of cells at the time of digestion. Pohl,[7] Erdely [8] and Hofmeister [9] gave a similar explanation, but felt that the source of the cells was in the lymph glands of the intestine. Froin [10] advanced the theory that the increased count in the periphery was not an indication of an actual increase in the number of cells, but was more in the nature of a mechanical transportation to the periphery. Viale and Di Leo Lira,[11] on the basis of their experiments, attribute this leukocytosis to the increase in the hydrochloric acid in the blood that they found during digestion.

WIDAL'S HEMOCLASTIC CRISIS

Still more numerous than the theories that account for the normal postprandial leukocytosis are the theories for the leukopenia that occasionally is found (Widal's hemoclastic crisis). Widal believes that this leukopenia is evidence of functional proteopexic hepatic deficiency, resulting in a symptom complex in which this condition, while the most easily obtained, is far from the most important. The theory that the phenomenon results from some abnormal mechanical transportation of the leukocytes has some supporters.[12]

Recently, a number of articles have been published in support of the possibility of an autonomic control of the peripheral leukocyte count and, consequently, a derangement of this system in those cases which show an abnormal response to stimulation.

Articles by Widal,[13] Müller and Petersen,[14] Tinel and Santenoise [15] are included in this list. Goudsmit [16] agrees, as far as autonomic control

5. Feinblatt, H. M.: Alimentary Leukocytosis in Various Pathologic Conditions, Arch. Int. Med. **33**:210 (Feb.) 1927. Holzer, P., and Schilling, E.: Ztschr. f. klin. Med. **93**:302, 1922.

6. Goodall, A., and Paton, D. N.: J. Physiol. **33**:20, 1905.

7. Pohl, J.: Arch. f. Exper. Path. u. Pharmakol. **20**:426, 1886.

8. Erdely: Ztschr. f. Biol. **46**:31, 1889.

9. Hofmeister, F.: Arch. f. Exper. Path. u. Pharmakol. **22**:306, 1887.

10. Froin, G.: Compt. rend. de Soc. de biol. **53**:311, 1907.

11. Viale, S., and Di Leo Lira, J.: Compt. rend. de Soc. de biol. **96**:228, 1927.

12. Worms, W., and Schrieber, H.: Ztschr. f. klin. Med. **93**:323, 1922.

13. Widal, F.; Abrams, P., and Lancovesco, N.: Presse méd. **28**:893, 1920.

14. Müller, E. F.: München. med. Wchnschr. **51**:1753, 1922. Müller, E. F., and Petersen, W. F.: Klin. Wchnschr. **6**:848, 1927.

15. Tinel, J., and Santenoise, D.: Compt. rend. de Soc. de biol. **85**:715, 1921.

16. Goudsmit, J.: Nederl. Tijdschr. u. Geneesk. **65**:41, 1922.

is concerned, but suggests further that the probable disturbance is in the balance of the blood colloids resulting from a deficiency in the liver. Glaser,[17] on the other hand, believes that the stimulating factors are the bile acids, and that their retention in hepatic deficiency is the probable explanation for the leukopenia and the changes in the blood that Widal has described. Holzer and Schilling[18] find that usually those cases which show gastric anacidity show a typical Widal curve, and they believe that the phenomena are in some way connected. Wollheim[19] has found that the variations in leukocytosis show a definite relation to the potassium calcium ratio of the blood, and can be modified by stimulation of the splanchnic and vagus nerves.

There must be some simple factor which will determine the leukocytic reaction of the periphery and the splanchnic region after the ingestion of food. Any explanation must give due regard to the following known phenomena:

1. There is a definite relation to alimentation, this relation being expressed in a series of actions and reactions (to correspond with the fluctuations of the peripheral count before the actual onset to digestive leukocytosis).

2. There is more or less uniformity in reaction to the different types of food.

3. There is greater instability and susceptibility in the reaction of children than adults.

4. Liver disease, asthma, anacidity and similar conditions will modify this factor.

SPLANCHNOPERIPHERAL BALANCE

Considerable work has been done recently as regards an autonomic balance between the periphery and the viscera. It has been shown[20] that during a chill, many of the phenomena are accounted for by the fixation of the autonomic system in one direction, the skin and the central organs showing opposite orientation. The liver, the spleen and the gastro-intestinal system all take a distinct part in this process. At the time of the chill, of course, the periphery is in a state of functional inhibition, and the leukocyte count is low. Undoubtedly, therefore, it is possible through the autonomic nervous system to affect a modification of the leukocyte count in the periphery.[21]

17. Glaser, F.: Med. Klin. **18**:688, 1922.

18. Holzer, P., and Schilling, E.: Berl. Klin. Wchnschr. **58**:1352, 1921

19. Wollheim, E.: Ztschr. f. d. ges. Exper. Med. **53**:287, 1926.

20. Petersen, W. F., and Müller, E. F.: The Splanchnoperipheral Balance During Chill and Fever, Arch. Int. Med. **40**:575 (Nov.) 1927.

21. Müller and Petersen (footnote 14). Müller, E. F.: Evidence of Nervous Control of Leukocytic Activity by Involuntary Nervous System, Arch. Int. Med. **37**:268 (Feb.) 1926.

The chill is a manifestation of a pathologic process. Whether or not a similar autonomic control is present during the fine fluctuations of the leukocyte count that take place physiologically is a debatable question. Since the gastro-intestinal tract plays an undoubted rôle in the general autonomic visceral reaction, it may well bear a relation to distribution of leukocytes, and of course, to the fluctuations in the count that take place during physiologic digestion. The stomach is the first part of the tract to be involved in active digestion and probably the portion most actively involved during the period of digestive leukocytosis. Following this train of thought, the conclusion was reached that a possible relation might exist between the tonus of the stomach and the peripheral capillaries, and the following experiments were carried out.

EXPERIMENTS

Experiments on Dogs.—(1) Leukocyte counts were made on the fasting animal every four or five minutes throughout the period of active hunger contractions.

(2) Leukocytes were counted in the starving animal during active hunger contractions, and the animal was shown food (psychic inhibition of hunger contraction).

(3) Leukocytes were counted in the fed animals with active digestive contractions throughout the period of digestion.

Experiments on Patients.—(4) Leukocytes were counted in patients with ulcers throughout the period of active hunger contractions and following the injection of a nonspecific milk preparation intramuscularly.

Method.—The dogs were trained to lie perfectly quiet without restraint throughout the experiment. Three of the animals used were gastrostomized three months before the experiment was carried out. A fine rubber balloon was passed into the stomach (by mouth or through fistula) at the end of the duodenal tube. The tube was connected with a water manometer, and the balloon was inflated with 80 cc. of air. The fluctuations of the manometer were then recorded on a slowly revolving kymograph.

A similar technic was employed in the patients. They were at complete rest in bed for one hour before and during the course of the experiment. One hundred and twenty cubic centimeters of air was used to inflate the balloon.[22]

Leukocyte counts were made at as frequent intervals as seemed necessary, under the usual standardized conditions. Blood from the ear was used.

---

22. I had some difficulty in the beginning in passing this balloon in patients. It was overcome by the following procedure: a few sticks of gelatin to which a little water has been added are heated over a water bath to the melting point. The balloon is dipped in this solution and rapidly twisted with the fingers until it forms practically a straight rod. It is allowed to dry in this position. Should it be necessary, another coat can be applied over the first, in the same manner. The patients experience little difficulty in swallowing this balloon, and when it reaches the stomach the gastric juice readily dissolves off the gelatin. After passing the tube, I waited two or three minutes to permit the gelatin to be removed; the tube was connected with a manometer, and the record taken as in dogs.

Results.—EXPERIMENT 1: As the stomach passed into a state of inhibition, following hunger contractions in the fasting animal, the peripheral leukocyte count fell and stayed down during the entire period of inhibition, to rise again as the stomach began to contract (chart 1).

EXPERIMENT 2. During the dilatation of the stomach induced by psychic stimulation in a starving animal, the leukocyte count dropped as the stomach dilated, and returned to its original level only when the stomach began to contract again (chart 2).

EXPERIMENT 3: During the period of digestive contractions, the tonus of the stomach was fairly constant, and similarly, the leukocyte count was constant (chart 3).

EXPERIMENT 4: In patients, the relaxation of tonus in a hungry patient occurring after the intramuscular injection of a nonspecific milk preparation was associated with a considerable leukopenia. Note, however, that this leukopenia became manifest, not at the time of injection, but at the time that the stomach dilated (chart 4).

COMMENT

From these results it would appear that the state of tone of the stomach is associated with distinct fluctuations in the peripheral leukocyte count. However, it is probably not the only factor. For example, it is known that injection of a nonspecific milk preparation, a protein substance, is followed by increased function and capillary dilatation in the liver.[23] I feel, therefore, that the dilation of the stomach which follows the injection of this substance is not a single response, but rather a part of the unified response of the entire splanchnic area.

Further, it is generally known that during active digestion, it is not only the stomach which is stimulated, but the entire splanchnic area.[24] If one assumes that the stomach reacts as a representative part of the viscera, one has in that organ a convenient method of determining the reaction of the splanchnic area of stimulation, and further, the relation between the splanchnic area and the peripheral organs. This so-called splanchnoperipheral balance[20] is therefore of importance in the controversial points of Widal's hemoclastic crisis. A chronic splanchnic pathologic condition will be associated with hyperemia of the liver, stomach, spleen and other organs, and in turn with catarrhal gastritis and delayed digestion. That means that in such a case the stomach will have to dilate more and longer than the normal stomach to accomplish the same physiologic end. Since gastric dilatation is closely interlinked with peripheral leukopenia the stomach which must dilate the longest will show the longest period of depression of the peripheral leukocyte count (Widal's hemoclastic crisis).

23. Müller and Petersen (footnote 14, second reference).

24. Ciacci, C., and Pizzini, B.: Arch. de méd. expér. et d'anat. path. **17**:129, 1905.

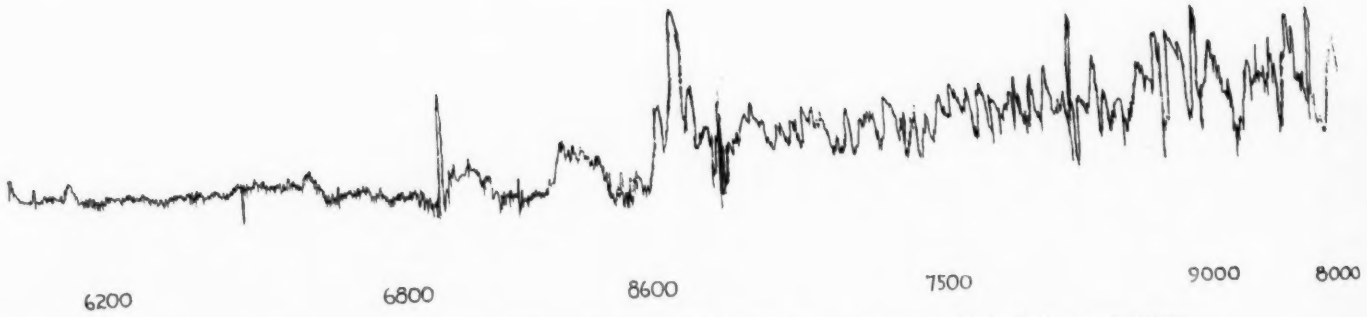


Chart 1.—Fasting animal; low leukocyte count during inhibition; increase of count with beginning contractions.

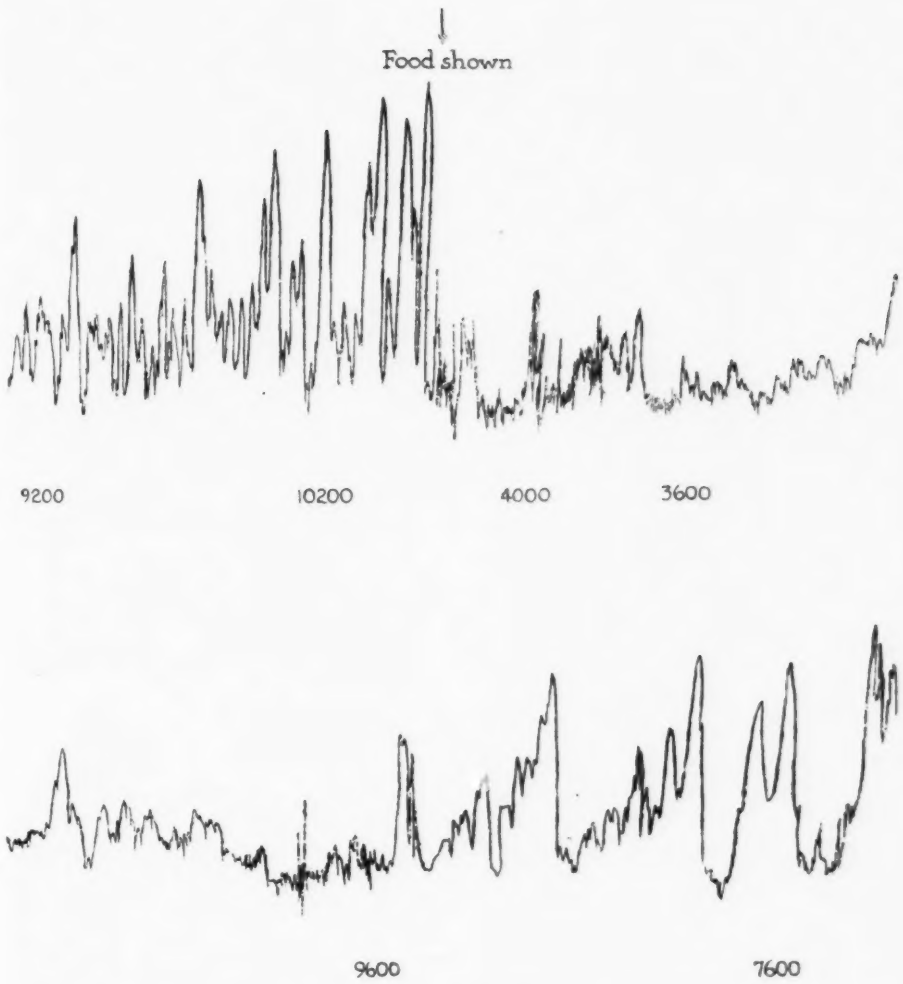
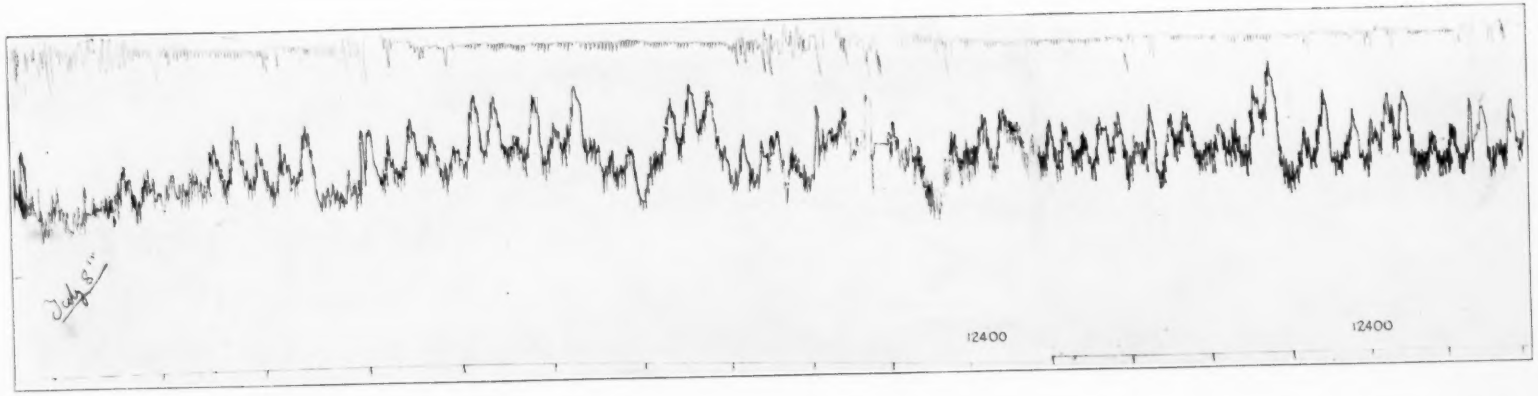
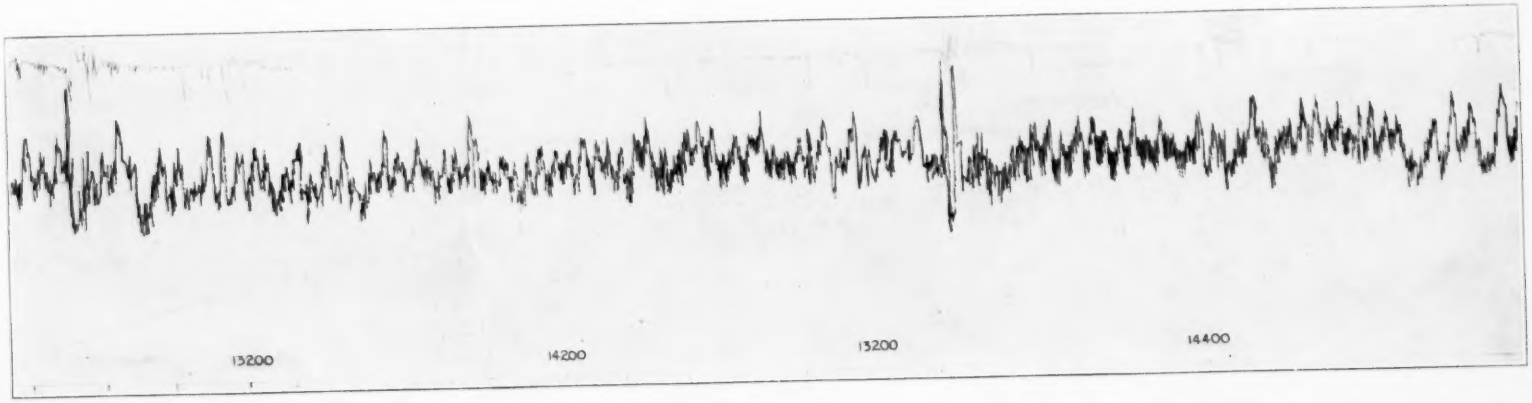
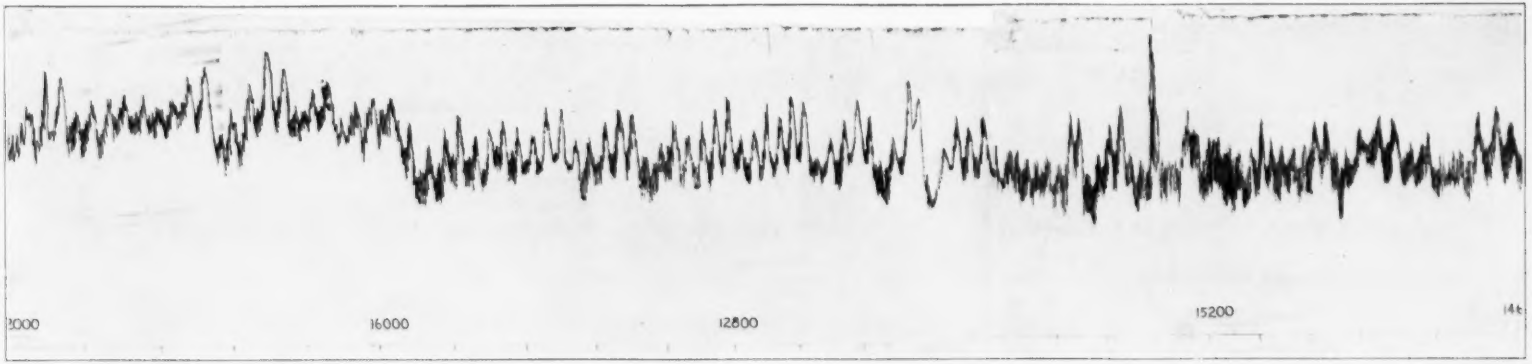


Chart 2.—Starving animal; primary period hunger contractions with high peripheral leukocyte count; psychic inhibition following the exhibition of food with immediate effect on the leukocyte count.


12400
12400


13200
14200
13200
14400



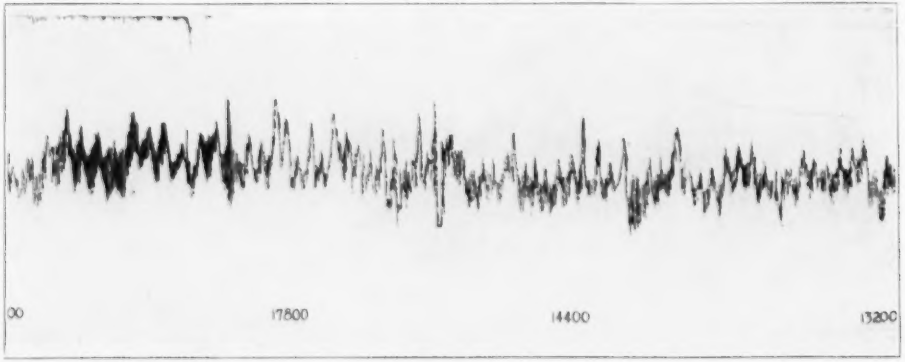


Chart 3.—Normal dog during digestive contractions; continued high leukocyte count.

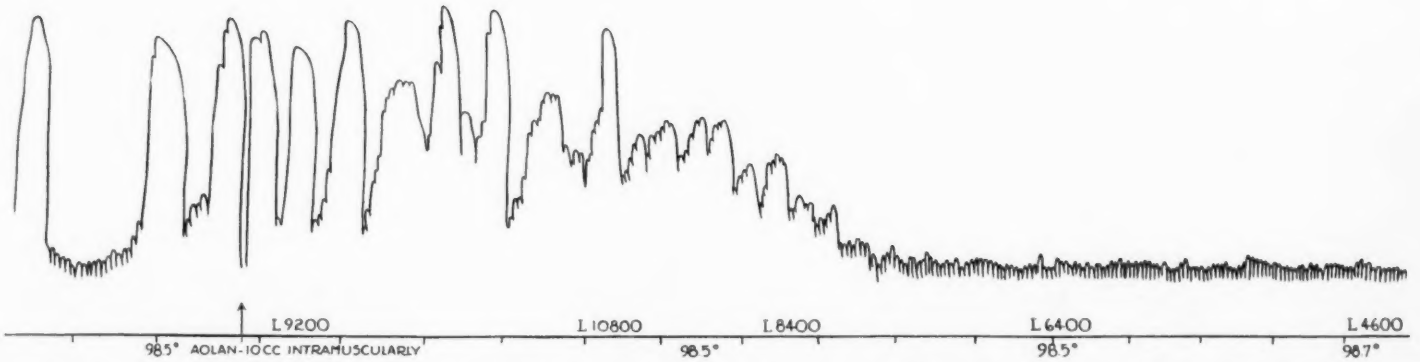


Chart 4.—Patient with gastric ulcer; hunger contractions with relatively high leukocyte count, leukopenia following injection of a nonspecific milk preparation together with coincident inhibition of stomach tonus.

Holzer and Schilling [18] have already shown that a typical Widal crisis will appear in every case that shows hypochlorhydria.

It would appear, therefore, that not only in liver disease, but in any splanchnic pathologic condition and probably in such diseases that are associated with autonomic inbalance (asthma, hay-fever, hyperpiesis and other conditions), a prolonged leukopenia will follow the ingestion of food—the result of the compensatory dilatation that the stomach must undergo in order to maintain its normal digestive function. At present I am attempting to obtain experimental proof for this hypothesis.

SUMMARY

1. There is a distinct time relationship between altered tonus of the stomach and alteration in the peripheral leukocyte count.

2. This relation is expressed as a leukocytosis when the stomach is actively contracting and a leukopenia during the period of gastric dilatation.

3. In those pathologic states that involve chronic gastric congestion, delayed digestion, one would expect a prolonged gastric dilatation to meet the physiologic digestive requirements, and consequently a prolonged leukopenia.

4. A discussion concerning how far the balance between the stomach and periphery depends on control through nervous, chemical or mechanical elements is not within the province of this paper.

Book Reviews

THE BELOVED PHYSICIAN, SIR JAMES MACKENZIE: A BIOGRAPHY. By R. MACNAIR WILSON. Price, $4.00. New York: The Macmillan Company, 1926.

There are many beloved physicians in every generation and Mackenzie well deserved the title for he was loved not only by those who saw in him the helpful physician, but by all who were first attracted by his investigating genius, and who came to know him personally. All these, and all who follow later in the study of medicine, will wish to learn all they can of Mackenzie, and will therefore be grateful for this biography. It is to be hoped that they will not be deterred by the strange style the author has cultivated, a combination of girl reporter and bed-time story teller. We get a brief but good account of Mackenzie's descent and early life and schooling, in which William Archer, the translator of Ibsen, appears as a classmate. The author makes much of the fact that Mackenzie was not a keen student in his early days. The impulse to study medicine, it is said, resulted from seeing the colored jars of water in a "chemist's" window—in American, pharmacist's. Mackenzie became an apprentice and for four years worked twelve hours a day in the pharmacy, with fifteen on Saturday and four on Sunday. This would horrify makers of medical school schedules, whose aim is to secure "time to think" for the present day student. Of course, Mackenzie was not formally a medical student then, and yet he had time to learn enough of the practical work and the fascination of the medical career to decide to take up the study, and this intention was not lessened during the year he spent after his apprenticeship, in a Glasgow pharmacy. At 21, he went to Edinburgh to begin medical work, four years older than the majority of the men of his "year." This was in 1874, the year Lister acknowledged his debt to Pasteur. In 1878, when Mackenzie got his degree, Pasteur delivered his address on wound putrefaction, and the young physician, thinking research as revealed by Pasteur was not for him, obtained a position as resident in the Edinburgh Royal Infirmary, as a preparation for general practice. In due time, he settled in the town of Burnley, in the "Black Country," where the first American pilgrims sought him out a few years later. The atmosphere of that Old World corner and the daily routine of Dr. Mackenzie's practice are well set forth by the author. How he took to research by following up the things his curiosity encountered in practice, is described in a provokingly rhetorical style; at least it seems so to a medically trained reader. Just how it affects the intelligent layman would be an interesting thing to investigate. It would be interesting, also, in a seminar in medical history to use the "Beloved Physician," allowing beginners to give their interpretation of the account there, having more advanced students work up Mackenzie's original publications and fitting together the two interpretations. It is unfortunate for medical readers that there is no bibliography. The various lines followed by Mackenzie in his further career are all described by the author, in the same artificial style. Through it all the personality of the man emphasizes itself, showing his power as an observer, a thinker and writer, and as a controversialist, but also his personal charm, a charm both physical and mental, and unusual sincerity and courage.

For the guidance of readers inexperienced in the history of medicine, it should be pointed out that certain exaggerations must be allowed for. The apathy with which Mackenzie's discoveries were received, the opposition he encountered, were not unusual or personal. Auenbrugger, who was no fighter, described the fate of all innovators in a few words. So there is a note of insincerity that Mackenzie, least of all subjects of biography, deserved in the

reiteration of the opposition of "the Giants," that is Mackenzie's seniors in practice, of their "roaring with mirth," of the man who was called a dunce at college, in fact merely called so by himself when at a secondary school. Certain things deserve more detailed mention than the author gives them. Hundreds of men before and after him used Dudgeon's sphygmograph. Some called it a toy and discarded it; some made uncalled for diagnoses on the ground of tracings well or badly made. Many hundreds saw also the motion of the jugular pulse. Mackenzie was almost the first to let his mind play on the phenomena, and was actually the first to employ a modification of the instrument and to advance the knowledge of disorders of the circulation. More might have been said of the apathy of professional investigators of physiology, although in time a few of them gave Mackenzie and the subject valuable assistance. Some of the neglect of simple examinations that Mackenzie complained of undoubtedly resulted from his own destructive criticism. That he had the human tendency to error appears from a quotation in chapter XXXII, in which he asserted that certain variations of the electrocardiogram are beyond interpretation. Perhaps they are, but the Mackenzie who put the funnel over the jugular vein would not have said so, he would have "tried," as he really did, through Thomas Lewis. Still another evidence is seen in his tendency to find "laws" for biologic phenomena, laws that may exist, but that have always eluded those who formally searched for them. The man and his investigations deserve the thoughtful consideration of all who concern themselves with the study of medicine, and the present work, with all its faults, will well repay the reader.

THE PHYSIOLOGY OF EXERCISE. A text-book for Students of Physical Education. By JAMES HUFF MCCURDY, A.M., M.D., M.P.E., Director of Physical Education Course in the International Young Men's Christian Association College, Springfield, Mass.; Editor of the American Physical Education Review. Second edition, thoroughly revised. Illustrated. Philadelphia: Lea & Febiger, 1928.

The subtitle of the book more nearly describes the character and aims of the book since it is essentially a textbook for students in physical education rather than a monograph on the physiology of exercise. The first half of the book is devoted to the general effects of exercise on bodily functions such as circulation, blood pressure, heart rate, blood composition, and the effects of exercise in the way of training and neuromuscular mechanism. The second part deals more specifically with the effects of certain types of exercise such as gymnastics, swimming, rowing and running on the bodily functions. There is a chapter on Physical Efficiency Tests and a concluding chapter on the Physiology of Training. Each chapter is concluded with a fairly complete bibliography and a detailed set of questions covering the content of each chapter. These questions appear like elementary examination questions.

The author appears conversant with the literature of the field, but the thorough assimilation in the presentation of the material frequently appears disappointing, the presentation being frequently merely a collection of statements by different authors without much analysis or critical fitting of these into the general scheme of the author. In many places the author appears in the rôle of a propagandist, exhorter or preacher for the benefits of physical training. At times he is guilty of loose or meaningless statements, like the following — "Woman is anabolic, while the man is catabolic in type." "The evolution of the animals has been physical development, that of man largely an intelligent and emotional one." Many of the questions appended at the end of each chapter appear too elementary, if not downright purile, to be included in a textbook on physical training for students of college grade. The following are examples: "Put on the board during the class session the normal resting horizontal and standing pulse of each member of the class." "What additional studies in blood pressure need to be made?" "What skeletal muscles are under splanchnic control and why?" "What studies

on the size of the heart in addition to the Harvard studies are needed?" "What are the effects of rowing in future life?"

The author makes a very telling albeit dubious point in favor of rowing by asserting (p. 220) "that Harvard oarsmen show a higher percentage of marriage and size of family than all the graduates of Princeton, Yale, Bowdoin and Harvard." And further, "the Harvard oarsmen are above the average in longevity, fecundity, health and success in life." The Who's Who in America is even brought in as evidence for this superior value of rowing to success. All this is interesting, but is it good science?

Despite these weaknesses or defects in the book, the volume will be found helpful to students of physical education and to doctors, in connection with exercise as a therapeutic measure, because of the presentation of the essential literature in compact and accessible form.

DISEASES OF THE MOUTH. By STERLING V. MEAD, D.D.S. Price, $10. Two hundred and seventy-four illustrations and 29 color plates. St. Louis: C. V. Mosby Company, 1927.

In his preface, the author notes the growing need for a "more intimate co-operation between dentists and physicians." A perusal of the text tends toward the conviction that such consultations are necessary, because neither physician nor dentist has the apparatus or experience required by the specialist in any branch of medicine other than his own; consequently, they must consult with each other, and each must record his observations. A review of the chapters on "Examination" points conclusively to the foregoing statements.

The chapter on "Impacted and Unerupted Teeth" is commendable in that it does not advocate the removal of such teeth without some definite reason for so doing; the judgment of both dentist and physician is frequently required before treatment should be instituted.

The chapter on "Pulpless Teeth" deals with the subject in a rational manner and deprecates treatment by the extraction faddist, as well as treatment by those who are opposed to extraction.

In the comprehensive chapter on "Stomatitis," page 329, I think a correction in priority should be made, namely, the term, "Ulceromembranous Gingivitis," as suggested by Grieves, is synonymous with "Acute Ulcerous Gingivitis" described by Dr. Thomas L. Gilmer in a paper published in the Dental Review, 1906, volume 19, page 459, and at his suggestion and from material furnished by him, Dr. Tunnicliff cultured, anaerobically, the organisms discovered and described by Vincent and Plant, thus demonstrating them as the cause of this disease.

This book will prove a valuable addition to the working library of both dentist and physician, as it brings out the multiplicity of diseases manifested in and about the mouth and will greatly assist the diagnostician, rather than the surgeon, as the size of the volume probably precludes the full discussion of pathology, technic and after-treatment.

EPIDEMIC INFLUENZA, A SURVEY. By EDWIN O. JORDAN, PH.D., SC.D., Professor of Hygiene and Bacteriology, The University of Chicago. Price, $5. Pp. 599 with 98 text figures. Chicago: American Medical Association, 1927.

The Committee on Scientific Research of the American Medical Association is to be congratulated on having secured the services of one so appropriately fitted as Professor Jordan to make a comprehensive survey of the literature on the last great influenza pandemic. He has examined most of the publications on the subject (his selected bibliography contains nearly 1,300 references) and has apparently done so with great care. His comments are critical and to the point; his conclusions are drawn with caution.

Jordan believes that the pandemic of 1918 was pretty certainly identical with that of 1890 and the other great pandemics of history; but that its relation

to the endemic disease diagnosed "influenza" and to the milder, more localized interpandemic epidemics of "influenza" is still an open question and is likely to remain so until their etiology is established. The voluminous statistical material on morbidity and mortality and the bearing on them of various social factors is reviewed at some length. The vexing problem of etiology and the rôle played by the secondary invaders are well discussed. Nothing of importance seems to have been added to the old descriptions of the clinical picture of the disease.

The final chapter deals with the various analyses which have been made of the epidemiologic data, and the theories which have been propounded to explain the occurrence of influenza pandemics. Jordan favors the theory of enhanced virulence of the virus as most easily explaining the facts which are at hand.

DIAGNOSIS AND TREATMENT OF DISEASES OF THE STOMACH, WITH AN INTRODUCTION TO PRACTICAL GASTRO-ENTEROLOGY. By MARTIN E. REHFUSS, M.D., Assistant Professor of Medicine at Jefferson Medical College. Cloth. Price, $12. Pp. 1236 with 519 illustrations, some in colors. Philadelphia: W. B. Saunders Company, 1927.

This volume deals entirely with diseases of the stomach and diseases of the gastro-intestinal tract in which definite gastric symptoms occur. The embryology, anatomy and physiology of the organ are considered briefly and in light of recent theories and research. Much of the author's original experimentation is included. Brief chapters are given to the consideration of special diagnostic procedures such as roentgen-ray examination. The consideration of clinical methods of diagnosis is, on the other hand, exhaustive. Several chapters in the book have been contributed by specialists in fields in which the technic or knowledge required for competency necessitates special training or experimentation.

The last half of the volume is given to the pure clinical description of gastric diseases. The author apparently feels the inaccuracy of the terminology employed in classifying many of these diseases. While adhering to the prevalent nomenclature, which as we know is not consistent in many instances with the most recent views in physiology, his consideration of disease is from the physiologic standpoint. These inconsistencies are carefully noted.

The suggested treatment of these diseases is also in concordance with the most recent scientific developments.

The book is recommended to those who desire a clinical treatise on gastric disease, based as far as is possible on scientific method. Certain sections of the book might be more concise. The statistical results following treatment might be considered more fully.

CANCER CONTROL. REPORT OF AN INTERNATIONAL SYMPOSIUM HELD UNDER THE AUSPICES OF THE AMERICAN SOCIETY FOR THE CONTROL OF CANCER, LAKE MOHONK, N. Y., SEPTEMBER 20-24, 1926. Pp. 336. Chicago: Surgical Publishing Company, 1927.

This volume of 336 pages represents the opinions of a large number of prominent authorities, both clinicians and laboratory workers, on all phases of the problem of lessening the mortality from cancer. One person in ten today is destined to die of cancer and one in five of those over 45.

Little new knowledge of the disease was reported at this meeting, and the discussions were mainly confined to generalities and problems of educating the laity and the family practitioner in the importance of early diagnosis and radical surgery. Radiotherapy was given but a limited field and then generally in the cases which were otherwise hopeless. The small fields of prevention in such pitifully few cases of cancer the etiology of which is known were dis-

cussed, and other highly controversial material was discussed but was considered unfit for general acceptance.

A favorable result in the campaign of the last few years is the increasing number of early curable cases, but much room for improvement is still present. Control by eugenic measures is today theoretically possible, but practically out of the question. The lead treatment is too new to pass judgment on, but it appears to have great possibilities.

The main accomplishment of the meeting was the organization of world-wide cooperation in the control of cancer.

DIE PHARMAZEUTISCHEN GRUNDLAGEN DER ARZNEIVERORDNUNGSLEHRE. VON GEORG EDMUND DANN. Price, 15 marks. Pp. 312, with tables, index and 10 illustrations. Leipzig: Theodor Steinkopff, 1927.

This book is a German edition of Gentz's "Der vanligare Läkemedelsformerna" subjected to some alterations and made to conform to the German panel regulations and pharmacopeia. Prescription writing is clearly described and illustrated by numerous examples which demonstrate how practically all of the useful pharmaceutic preparations may be applied in practice. More than half of the book is taken up with worth while tables of dosages, solubilities, incompatibilities, explosive mixtures and so on; the list of antidotes, however, is not entirely modern.

The book is well printed and may be recommended to those interested in this phase of therapeutics.

THE TEXTBOOK OF MEDICINE. By A. S. BLUMGARTEN, M.D. Price, $3. Pp. 530. New York: The MacMillan Company, 1927.

This book is written for nurses. It is well outlined, concise and complete. Only the material essential to the nurse is discussed in any particular disease, and enough physiology and pathology is included to make things well understood. The therapy in some cases seems as though it might be a little misleading, as many drugs and procedures are mentioned or discussed which probably are of little value. The book, however, has been carefully written and will rank among the best textbooks for nurses.

INDEX TO VOLUME 41

PAGE

Acromegaly, and diabetes 883
antagonism between insulin and pituitary extract; its demonstration in patient with 875
Adkinson, J.: Bacteriologic examination of 724 sputums from as many patients with bronchial asthma 601
Agranulocytosis: See Angina, agranulocytic
Albuminuria, urinary proteins not originating in blood 445
Alkalis and renal injury 10
on secretion and composition of gastric juice, influence of; effect of sodium bicarbonate on the gastric response to histamine 244
Allen, E. A.: Culture methods, encystment and excystment of councilmania dissimilis Kofoid, in culture 574
Alvarez, W. C.: Intestinal absorption 112
Ameba, culture methods, encystment and excystment of councilmania dissimilis Kofoid in culture 558, 574, 579
Anaphylaxis, hypersensitiveness or allergy in 5 generations of one family, occurrence of 472
studies in asthma; an analysis of 213 cases in which patients were relieved for more than 2 years 346
Andrews, E.: Urinary proteins not originating in blood 445
Anemia, experimental, produced by clostridium welchii; chemical analysis of blood 370
pernicious, hemocidal properties of blood serum; with special reference to 482
Angina, agranulocytic; report of case 343
Angina Pectoris; syndrome caused by anoxemia of myocardium 769
Aorta, coarctation of 702
Arquin, S.: Stomach tonus and peripheral leukocyte count (splanchnoperipheral balance) 913
Asthma: See also Anaphylaxis
and related allergic diseases, roentgen-ray treatment of spleen in 683
bronchial, bacteriologic examination of 724 sputums from as many patients with 601
studies in; an analysis of 213 cases in which patients were relieved for more than 2 years 346
Ayman, D.: Sublingual absorption of drugs; morphine 231

Bacillus coli, active immunization against experimental B. coli in peritonitis 42
Bacteria, clostridium welchii, experimental anemia produced by; chemical analysis of the blood 370
Bacteriophagy, in urinary infections following administration of bacteriophage therapeutically 189
Bang, S.: Fever in gastric and duodenal ulcer 808
Bassler, A.: The iodine-starch test of body fluids. Deductions from over 100 consecutive tests of external secretion of pancreas in diabetes, in diseases of the gallbladder and pancreas, and in a normal condition 18
Biloon, S.: Synthalin; its use in treatment of diabetes 453
Binswanger, H. F.: Effect of emotion on basal metabolism 834
Blackford, L. M.: Coarctation of the aorta 702
Block, L.: Plasma and corpuscular chlorides in peptic ulcer 415
Blood, auscultatory gap in sphygmomanometry 249

PAGE

Blood—Continued
chemical changes in blood in mercuric chloride poisoning; mechanism and significance of hypochloremia 234
chlorides, plasma and corpuscular in peptic ulcer 415
nonprotein sulphur of, in certain pathologic conditions 385
pressure, hypertensive encephalopathy 264
pressure, malignant hypertension, syndrome of 141
proteins, urinary, not originating in 428
serum, hemocidal properties of; with special reference to pernicious anemia. 482
stomach tonus and peripheral leukocyte count (splanchnoperipheral balance) 913
sugar, of normal human blood, variations in reducing power 586
Boas, E. P.: Cardiotachometer; an instrument to count the totality of heart beats over long periods of time 403
Bolliger, A.: Renal function tests with sodium thiosulphate and sodium iodide; experimental comparison with phenolsulphonphthalein test 642
Boyd, T. E.: Influence of alkalis on secretion and composition of gastric juice; effect of sodium bicarbonate on gastric response to histamine 244
Boyers, L. M.: Presentation of case of infection with councilmania dissimilis Kofoid 579

Book Reviews:
Avitaminosen und Verwandte Krankheitszustände; Herausgegeben von W. Stepp and P. György 138
Clinical Physiology in Relation to Modern Diagnosis and Treatment; R. J. S. McDowell 292
Das Versagen Des Kreislaufes. Dynamische und Energetische Ursachen; Von Prof. H. Eppinger 293
Diagnosis and Treatment of Diseases of the Stomach, with an introduction to Practical Gastro-Enterology; M. E. Rehfuss 927
Die Pharmazeutischen Grundlagen der Arzneiverordnungslehre; G. E. Dann .. 928
Diseases of the Digestive Organs with Special Reference to Their Diagnosis and Treatment; C. D. Aaron, ed. 4 revised 140
Diseases of the Mouth; S. V. Mead 926
Endokrine Krankheiten; H. Curschmann. 614
Epidemic Influenza; a Survey; E. O. Jordan 926
Hypotension; A. Friedlander 767
Innere Sekretion. Ihre Physiologie, Pathologie und Klinik; Von Dr. Julius Bauer 137
Introduction to the Study of Experimental Medicine; C. Bernard. (Translated under the auspices of the General Educational Board, by H. Copley Green, A.M.), introduction by L. J. Henderson 139
Medical Department of the United States Army in the World War: Vol. II. Administration American Expeditionary Force 294
Medizinische Praxis — Sammlung fur Arztliche Fortbildung. Volume 2—Die Magengeschwurskrankheit — Pathologie und Therapie Standpunkt des Internisten; H. Ohnell 768
Modern Medicine, Its Theory and Practice; Edited by Sir William Osler. Re-edited by T. McCrae and E. H. Funk. Volumes 4 and 5 766

PAGE

Book Reviews—Continued
Modern Practice of Pediatrics; W. P. Lucas 294
Pioneer Medicine in Western Pennsylvania; T. Diller 767
Scientific Reports of the Government Institute for Infectious Diseases; The Imperial University 293
Sklerose und Hypertonie der Innervierten Arterien; G. Ricker 767
The Beloved Physician; Sir J. Mackenzie; A Biography 924
The Harvey Lectures, 1925-1926. Series 21 764
The Normal Chest; J. A. Myers 139
The Normal Diet; W. D. Sansum 768
The Physiology of Exercise; J. H. McCurdy 925
The Text Book of Medicine; A. S. Blumgarten 928
Brown, E.: Blood volume in edema of glomerular nephritis and nephrosis 44
Buchman, T. E.: Hemocidal properties of the blood serum; with special reference to pernicious anemia 482

Caldwell, J. A.: Bacteriophagy in urinary infections following administration of bacteriophage therapeutically 189
Cardiotachometer; an instrument to count the totality of heart beats over long periods of time 403
Cecil, R. L.: The specific treatment of lobar pneumonia 295
Chlorides, in blood: See blood chlorides
Chondroma: See Tumors, chondroma
Clostridium: See Bacteria
Coarctation of aorta 702
Colitis, chronic ulcerative with reference to bacterial etiology; experimental studies 75
Collen, W. S.: Mumps polyneuritis; quadriplegia with bilateral facial paralysis 61
Cordero, N.: Influence of posture on phenolsulphonphthalein test for kidney function 279
Councilmania tenuis and C. dissimilis, intestinal amebas of man; report of case 558, 574, 579
Cutten, C.: The Icterus Index; spectrophotometric and quantitative studies ... 428

Davis, D.: Sublingual absorption of drugs; morphine 231
Denis, W.: Nonprotein sulphur of blood in certain pathologic conditions 385
Dextrose, tolerance, effect of toxemia on .. 257
Diabetes, and acromegaly 883
Diabetes, Mellitus; deductions from over 100 consecutive tests of external secretion of pancreas in diabetes, diseases of gallbladder and pancreas and in normal condition; iodine-starch test of body fluids 18
synthalin in the treatment of 453
Dock, W.: The reciprocal rhythm; report of case in which auricular tachycardia with partial a-v dissociation and atrioventricular bradycardia, with reciprocating rhythm, were present 745
Drugs, effect on cardiac output; effect of ephedrine on the minute cardiac output of normal dogs 622
Duodenum, ulcer: See Peptic Ulcer
Dunn, H. L.: A record system suitable for both clinical and statistical medicine .. 499

Edema, glomerular nephritis and nephrosis of, and blood volume in 44
Emerson, E. E.: The icterus index; spectrophotometric and quantitative studies 428
Encephalopathy, hypertensive 264
Ephedrine, effects of, on the minute cardiac output of normal dogs; effects of drugs on cardiac output 622
Extremities, lower, effect on basal metabolism of ligating 655

PAGE

Eyster, J. A. E.: Determination of cardiac hypertrophy by roentgen-ray methods .. 667
Feldman, A.: The intradermal salt solution test in nephritis in adults 102
The intradermal salt solution test in tuberculosis 549
Felsen, J.: Chondroma of spine associated with a transverse myelitis 736
Fishberg, A. M.: Hypertensive encephalopathy 264
Fisher, W. S.: Chemical changes in blood in mercuric chloride poisoning; mechanism and significance of hypochloremia . 234
Friedman, M. H.: Influence of posture on phenolsulphonphthalein test for kidney function 279

Gallbladder, congenital malformations of; report of 3 cases observed by cholecystography 198
deductions from over 100 tests of the external secretion of pancreas in diabetes, in diseases of gallbladder and pancreas, and in a normal condition; iodine-starch test of body fluids 18
Gastro-Intestinal Tract, influence to alkalis on secretion and composition of gastric juice; effect of sodium bicarbonate on gastric response to histamine 244
Goldblatt, H.: Peritonitis; active immunization against experimental B. coli peritonitis 43
Gundrum, L. K.: Agranulocytic angina; report of a case 343

Halley, C. R. L.: Second infection in syphilis; its relation to time of treatment to first infection 843
Harris, M. M.: Synthalin; its use in the treatment of diabetes 453
Harrison, T. R.: Effects of drugs on cardiac output; effect of ephedrine on the minute output of normal dogs 622
Heart, angina pectoris; syndrome caused by anoxemia of myocardium 769
determination of cardiac hypertrophy by roentgen-ray methods 667
effects of drugs on cardiac output; effects of ephedrine on the minute cardiac output on normal dogs 622
report of case in which auricular tachycardia with partial a-v dissociation and atrioventricular bradycardia, with reciprocating, rhythm, were present 745
Heimbeck, J.: Immunity to tuberculosis ... 336
Herrmann, G. R.: Nonprotein sulphur of blood in certain pathologic conditions .. 385
Horrall, O. H.: Hemocidal properties of the blood serum; with special reference to pernicious anemia 482
Hosoi, K.: Intestinal absorption 112
Hufford, A. R.: Elective localization of streptococci isolated from cases of peptic ulcer 210
Hypertension: See Blood Pressure
Hypersensitiveness: See Anaphylaxis

Icterus Index, spectrophotometric and quantitative studies 428
Tuberculosis, immunity to 336
Instruments: See under names of instruments as Cardiotachometer
Intestines, absorption of; a search for a low residue diet 112
councilmania tenius and C. dissimilis, intestinal amebas of man 558, 574, 579
intestinal digestion and pancreatic function, study of 867
Insulin, and pituitary extract, antagonism between; demonstration in patient with acromegaly 875
effect of toxemia on tolerance for dextrose and on action of 420
Iodine, compounds; their selective absorption by hyperplastic thyroid gland of dog ... 615
effect on toxic adenoma 66

PAGE

Iodine—Continued
renal function tests with sodium thiosulphate and sodium iodide; experimental comparison with phenolsulphonphthalein test ... 642
Iodine, test of body fluids with iodine-starch; deductions from over 100 consecutive tests of external secretion of pancreas in diabetes, diseases of gall-bladder and pancreas and in normal condition ... 18

Jaundice, obstructive, experimental; modification of parathyroid tetany mechanism in jaundice ... 754

Kampmeier, R. H.: Effect of iodine in toxic adenoma ... 66
Kast, L.: Experimental anemia produced by clostridium welchii; chemical analysis of blood ... 370
Keefer, C. S.: Angina pectoris; syndrome caused by anoxemia of myocardium ... 769
Keith, N. M.: The syndrome of malignant hypertension ... 141
Kernohan, J. W.: The syndrome of malignant hypertension ... 141
Kidney, alkalis and renal injury ... 10
function, influence of posture on phenolsulphonphthalein test for ... 279
renal function tests with sodium thiosulphate and sodium iodide; experimental comparison with phenolsulphonphthalein test ... 642
Killian, J. A.: Experimental anemia produced by clostridium welchii; chemical analysis of blood ... 370
Kofoid, C. A.: Concilmania tenuis and C. dissimilis, intestinal amebas of man ... 558

Lackey, R. W.: Effect of toxemia on tolerance for dextrose ... 257
Landy, A.: Synthalin; its use in treatment of diabetes ... 453
Levine, S.: Congenital malformations of the gallbladder; report of 3 cases observed by cholecystography ... 198
Logarithmic tables for computing the surface area of the body according to Dubois formula ... 97

McCloy, C. H.: Logarithmic tables for computing the surface area of the body according to Dubois formula ... 97
MacCarty, W. C.: Chronic splenomegaly ... 536
Mann, F. C.: Intestinal absorption ... 112
Mercuric Chloride, poisoning, chemical changes in blood in; mechanism and significance of hypochloremia ... 234
Metabolism, basal; basal metabolic rate in relation to symptoms and signs in hyperthyroidism ... 830
basal; correlation of basal metabolic rate and basal pulse rate ... 663
basal, effect of emotion on ... 834
basal, of ligating lower extremities, effect on ... 655
Mudd, S. G.: Auscultatory gap in sphygmomanometry ... 249
Mulier, H.: Effect on basal metabolism of ligating lower extremities ... 655
Mumps: See Parotitis
Myelitis, transverse, chondroma of spine associated with ... 736

Nephritis, glomerular nephritis and nephrosis edema of, and blood volume in ... 44
in adults, the intradermal salt solution test in ... 102
Nickel, A. C.: Elective localization of streptococci isolated from cases of peptic ulcer ... 210

Oppenheimer, B. S.: Hypertensive encephalopathy ... 264

Page, I. H.: Streptothrix necrotic bronchopneumonia ... 127

PAGE

Pancreas, deductions from over 100 consecutive tests of external secretion of pancreas in diabetes, diseases of gall-bladder and pancreas and in a normal condition; iodine-starch test of body fluids ... 18
pancreatic function and upper intestinal digestion; study of ... 867
Paralysis, quadriplegia with bilateral facial in polyneuritic mumps ... 61
Parotitis, mumps polyneuritis; quadriplegia with bilateral facial paralysis ... 61
Patterson, M. B.: Experimental anemia produced by clostridium welchii; chemical analysis of blood ... 370
Paulson, M.: Chronic ulcerative colitis with reference to bacterial etiology; experimental studies ... 75
Peptic Ulcer, elective localization of streptococci isolated from cases of ... 210
fever in gastric and duodenal ulcer ... 808
plasma and corpuscular chlorides in ... 415
observations on behavior of stomach and duodenum in presence of pain ... 633
Peritonitis; active immunzition against experimental B. coli in ... 12
Phenolsulphonphthalein Test, for kidney function, influence of posture on ... 279
Pierce, H. F.: Variations in reducing power (sugar) of normal human blood ... 586
Pilcher, C.: Effects of drugs on cardiac output; effect of ephedrine on the minute cardiac output of normal dogs ... 622
Pituitary, extract and insulin, antagonism between; demonstration in patient with acromegaly ... 875
Pneumonia, lobar, specific treatment of ... 295
streptothrix necrotic bronchopneumonia ... 127
Polyneuritis, mumps; quadriplegia with bilateral paralysis ... 61
Proteins, in urine: See Albuminuria

Rabinowitz, A.: Mumps polyneuritis; quadriplegia with bilateral facial paralysis ... 61
Rackemann, F. M.: Studies in asthma; an analysis of 213 cases in which patients were relieved for more than 2 years ... 346
Reed, L.: Nonprotein sulphur of blood in certain pathologic conditions ... 385
Reifsneider, J. S.: The intradermal salt solution test in nephritis in adults ... 102
Resnik, W. H.: Angina Pectoris; syndrome caused by anoxemia of the myocardium ... 769
Rhythm, gallop, the clinical significance of ... 1
Richardson, C. L.: Chemical changes in blood of mercuric chloride poisoning; mechanism and significance of hypochloremia ... 234
Ringer, A. I.: Synthalin; its use in treatment of diabetes ... 453
Rockwell, R.: A record system suitable for both clinical and statistical medicine ... 499
Roentgen Rays, methods, determination of cardiac hypertrophy by ... 667
treatment of spleen in asthma and in related allergic diseases ... 683
Rosenthal, S. M.: Pancreatic function and upper intestinal digestion; study of ... 867
Rowntree, G.: Blood volume in edema of glomerular nephritis and nephrosis ... 44

Schlegel, K. W.: Urinary proteins not originating in blood ... 445
Scott, E. L.: Variations in reducing power (sugar) of normal human blood ... 586
Segal, H. L.: Effect of emotion on basal metabolism ... 834
Serby, A. M.: Plasma and corpuscular chlorides in peptic ulcer ... 415
Smith, A. E.: Occurrence of hypersensitiveness or allergy in 5 generations of one family ... 472

PAGE

Smith, J. H.: Basal metabolism; basal metabolic rate in relation to symptoms and signs in hyperthyroidism 830
Basal metabolism; correlation of basal metabolic rate and basal pulse rate 663
Sodium bicarbonate on gastric response to histamine, effect of; influence of alkalis on secretion and composition of gastric juice 244
Sodium Iodide: See under iodine
Sodium Thiosulphate: See Thiosulphate
Sphygmomanometry, auscultatory gap in ... 249
Spine, associated with a transverse myelitis, chondroma of 736
Splenomegaly, chronic 536
Sputum, bacteriologic examination of, from 724 patients with bronchial asthma 601
Steinberg, B.: Peritonitis; active immunization against experimental B. coli peritonitis 42
Stieglitz, E. J.: Alkalis and renal injury .. 10
Stomach, tonus, and peripheral leukocyte count (splanchnoperipheral balance) ... 913
Streptococcus, elective localization of, islated from cases of peptic ulcer 210
Streptothrix, necrotic bronchopneumonia 127
Strouse, S.: Effect of emotion on basal metabolism 834
Sublingual absorption of drugs; morphine .. 231
Sweeney, J. S.: The effect of toxemia on tolerance for dextrose 257
Synthalin; its use in the treatment of diabetes 453
Syphilis, second infection in; its relation to time of treatment of first infection 843

Tetany, parathyroid, mechanism in jaundice modification of; experimental obstructive jaundice 754
Thiosulphate, sodium and sodium iodide, renal function tests with; experimental comparison with the phenolsulphonphthalein test 642
Thomas, W. A.: Urinary protein not originating in blood 445
Thyroid, basal metabolism; basal metabolic rate in relation to symptoms and signs in hyperthyroidism 830
iodine compounds; their selective absorption by hyperplastic thyroid gland of dog 615

PAGE

Topper, A.: Effect on basal metabolism of ligating lower extremities 655
Toxemia, on tolerance for dextrose and action of insulin, effect of 257, 420
Trusler, H. M.: Chemical changes in blood in mercuric chloride poisoning; mechanism and significance of hypochloremia 234
Tuberculosis, immunity to 336
intradermal salt solution test in 549
Tumors, chondroma of spine associated with transverse myelitis 736
effect of iodine on toxic adenoma 66

Ulrich, H.: Antagonism between insulin and pituitary extract 875
Urine, urinary proteins not originating in blood 445

Van Dyke, H. B.: Iodine compounds; their selective absorption by hyperplastic thyroid gland of dog 615
Vital Statistics, record system suitable for both clinical and statistical medicine .. 499

Wagener, H. P.: The syndrome of malignant hypertension 141
Waldbott, G. L.: Roentgen-ray treatment of spleen in asthma and in related allergic diseases 683
Walker, I. C.: Bacteriologic examination of 724 sputums from as many patients with bronchial asthma 601
Wasserman, H.: Second infection in syphilis; its relation to time of treatment of first infection 843
White, P. D.: Auscultatory gap in sphygmomanometry 249
The clinical significance of gallop rhythm . 1
Wilson, C. P.: Effects of drugs on cardiac output; effect of ephedrine on the minute output of normal dogs 622
Wilson, M. J.: Duodenal ulcer; observations on behavior of stomach and duodenum in the presence of pain 633
Woodruff, W.: Icterus index; spectrophotometric and quantitative studies 428

Yater, W. M.: Acromegaly and diabetes; report of 6 cases 883
Youmans, J. B.: Effect of iodine in toxic adenoma 66

Medical Library
JUN 27 1928

VOLUME 41 NUMBER 6

ARCHIVES
OF
INTERNAL MEDICINE

EDITORIAL BOARD

JOSEPH L. MILLER, Chicago

RICHARD C. CABOT, Boston — WARFIELD T. LONGCOPE, Baltimore

GEORGE DOCK, Pasadena, Calif. — WALTER W. PALMER, New York City

W. S. THAYER, Baltimore

JUNE, 1928

PUBLISHED MONTHLY BY AMERICAN MEDICAL ASSOCIATION, 535 NORTH DEARBORN STREET, CHICAGO, ILLINOIS. ANNUAL SUBSCRIPTION, $5.00

Entered as Second-Class Matter, January 23, 1909, at the Postoffice at Chicago, Illinois, Under Act of Congress of March 3, 1879. Acceptance for mailing at special rate of postage provided for in Section 1103, Act of October 3, 1917, authorized on June 14, 1918.

COPYRIGHT, 1928, BY THE AMERICAN MEDICAL ASSOCIATION

THE ARCHIVES OF INTERNAL MEDICINE is published by the American Medical Association for the advancement of scientific medicine in the United States and as a medium of publication for research and observation in the domain of internal medicine.

Manuscripts for publication, books for review, and correspondence relating to the editorial management should be sent to Dr. Joseph L. Miller, Editor-in-Chief, 122 South Michigan Boulevard, Chicago, or to any other member of the Editorial Board. Communications regarding subscriptions, reprints, etc., should be addressed, ARCHIVES OF INTERNAL MEDICINE, American Medical Association, 535 North Dearborn Street, Chicago.

Articles are accepted for publication on condition that they are contributed solely to the ARCHIVES OF INTERNAL MEDICINE. Manuscripts must be typewritten, preferably double spaced, and the original copy should be submitted. Zinc etchings and halftones of illustrations will be supplied by the Association when the original illustrations warrant.

Footnotes and bibliographies should conform to the style of the Quarterly Cumulative Index Medicus, published by the American Medical Association. This requires, in order given: name of author, title of article, name of periodical, with volume, page, month—day of month if weekly—and year. A complete list of abbreviations for standard periodicals, together with a full discussion of the style of the A. M. A. publications, appears in The Art and Practice of Medical Writing, a comprehensive book on the preparation of medical manuscripts, published by the American Medical Association. Price, $1.50.

Matter appearing in the ARCHIVES OF INTERNAL MEDICINE is covered by copyright but, as a rule, no objection will be made to its reproduction in reputable medical journals, if proper credit is given. However, the reproduction for commercial purposes of articles appearing in the ARCHIVES OF INTERNAL MEDICINE, or in any of the other publications issued by the Association, will not be permitted.

Authors will receive one hundred reprints free; additional reprints may be obtained at cost.

The ARCHIVES OF INTERNAL MEDICINE is published monthly. Annual subscription price (two volumes): Domestic, $5.00; Canadian, $5.40; foreign, $5.75, including postage. Single copies, 75 cents, postpaid.

Checks, etc., should be made payable to the AMERICAN MEDICAL ASSOCIATION.

OTHER PERIODICAL PUBLICATIONS

of the American Medical Association

THE JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION—Weekly. Covers all the medical sciences and matters of general medical interest. Illustrated. Annual subscription price (two volumes): Domestic, $5.00; Canadian, $6.50; foreign, $7.50. Single copies, 20 cents.

AMERICAN JOURNAL OF DISEASES OF CHILDREN—Monthly. Presents pediatrics as a medical science and as a social problem. It includes carefully prepared collective abstracts based on recent pediatric literature, abstracts from foreign and domestic literature, book reviews, society transactions, etc. Illustrated. Annual subscription price (two volumes): Domestic, $5.00; Canadian, $5.40; foreign, $5.75. Single copies, 75 cents.

ARCHIVES OF NEUROLOGY AND PSYCHIATRY—Monthly. A medium for the presentation of original articles on nervous and mental diseases, with abstracts from foreign and domestic literature, book reviews, society transactions, etc. Illustrated. Annual subscription price (two volumes): Domestic, $8.00; Canadian, $8.40; foreign, $8.75. Single copies, 85 cents.

ARCHIVES OF DERMATOLOGY AND SYPHILOLOGY—Monthly. Devoted to advancing the knowledge of and progress in cutaneous diseases and syphilis. Publishes original contributions and full abstracts of the literature on these two subjects, transactions of the important dermatological societies, book reviews, etc. Illustrated. Annual subscription price (two volumes): Domestic, $8.00; Canadian, $8.40; foreign, $8.75. Single copies, 85 cents.

ARCHIVES OF SURGERY—Monthly. Devoted largely to the investigative and clinical phases of surgery, with monthly reviews on orthopedic and urologic surgery. Well illustrated. Annual subscription price (two volumes): Domestic, $3.00; Canadian, $8.40; foreign, $3.75. Single copies, 85 cents.

ARCHIVES OF OTOLARYNGOLOGY—Monthly. A medium for the presentation of original articles on diseases of the ear, nose and throat, with abstracts from foreign and domestic literature, book reviews, the transactions of special societies, etc. Illustrated. Annual subscription price (two volumes): Domestic, $6.00; Canadian, $6.40; foreign, $6.75. Single copies, 75 cents.

ARCHIVES OF PATHOLOGY—Monthly. A periodical devoted to the publication of original contributions in the field of pathology, with abstracts from foreign and domestic literature, book reviews, the transactions of special societies, etc. Illustrated. Annual subscription price (two volumes): Domestic, $6.00; Canadian, $6.40; foreign, $6.75. Single copies, 75 cents.

QUARTERLY CUMULATIVE INDEX MEDICUS—Quarterly. A complete subject and author index to the worth-while current medical literature of the world. Issued four times a year. Second and fourth volumes bound for permanent reference. Subscription price, calendar year: Domestic, $8.00; Canadian, $8.50; foreign, $8.75.

AMERICAN MEDICAL ASSOCIATION

535 North Dearborn St. CHICAGO

CONTENTS

PAGE

ANGINA PECTORIS: A SYNDROME CAUSED BY ANOXEMIA OF THE MYOCARDIUM. CHESTER S. KEEFER, M.D., CHICAGO, AND WILLIAM H. RESNIK, M.D., STAMFORD, CONN. 769

FEVER IN GASTRIC AND IN DUODENAL ULCER. SOPHUS BANG, M.D., COPENHAGEN, DENMARK 808

BASAL METABOLISM: II. THE BASAL METABOLIC RATE IN RELATION TO SYMPTOMS AND SIGNS IN HYPERTHYROIDISM. JAMES H. SMITH, M.D., RICHMOND, VA. 830

THE EFFECT OF EMOTION ON BASAL METABOLISM. HARRY L. SEGAL, M.D.; HERBERT F. BINSWANGER, M.D., AND SOLOMON STROUSE, M.D., CHICAGO 834

SECOND INFECTION IN SYPHILIS: ITS RELATION TO THE TIME OF TREATMENT OF THE FIRST INFECTION. CHARLES R. L. HALLEY, M.D., WASHINGTON, D. C., AND HARRY WASSERMAN, M.D., BALTIMORE 843

PANCREATIC FUNCTION AND UPPER INTESTINAL DIGESTION: A NEW METHOD OF STUDY. SANFORD M. ROSENTHAL, M.D., MONTREAL 867

THE ANTAGONISM BETWEEN INSULIN AND PITUITARY EXTRACT: ITS DEMONSTRATION IN A PATIENT WITH ACROMEGALY. HELMUTH ULRICH, M.D., BOSTON 875

ACROMEGALY AND DIABETES: REPORT OF SIX CASES. WALLACE M. YATER, M.D., ROCHESTER, MINN. 883

STOMACH TONUS AND PERIPHERAL LEUKOCYTE COUNT (SPLANCHNOPERIPHERAL BALANCE). SERGIUS ARQUIN, M.D., CHICAGO 913

BOOK REVIEWS 924

GENERAL INDEX 929